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- (73) Proprietor: **IMPERIAL CHEMICAL INDUSTRIES PLC**
Imperial Chemical House,
Millbank
London SW1P 3JF (GB)
- Proprietor: **NATIONAL RESEARCH DEVELOPMENT CORPORATION**
101 Newington Causeway
London SE1 6BU (GB)

- (72) Inventor: **Hughes, Leslie Richard**
11 Clarendon Drive
Macclesfield Cheshire, SK10 2QQ (GB)
Inventor: **Oldfield, John**
68 Hallwood Road
Handforth Wilmslow Cheshire (GB)
Inventor: **Pegg, Stephen John**
22 Appleby Close
Macclesfield Cheshire, SK11 8XB (GB)
Inventor: **Barker, Andrew John**
58 Ullswater
Macclesfield Cheshire, SK10 7YW (GB)
Inventor: **Marshall, Peter Robert**
98 Vernon Road
Poynton Cheshire, SK12 1YR (GB)
- (74) Representative: **Tait, Brian Steele et al**
ICI Group Patents Service Dept.
PO Box 6
Shire Park
Bessemer Road
Welwyn Garden City Herts AL7 1 HD (GB)

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Description

This invention relates to novel anti-tumour agents and more particularly it relates to quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity. The invention includes novel quinazoline derivatives and processes for their manufacture; novel pharmaceutical compositions containing said quinazoline derivatives and the use of said quinazoline derivatives in the manufacture of novel medicaments for use in the production of an anti-tumour effect in a warm-blooded animal such as man.

One group of anti-tumour agents comprises the antimetabolites, such as aminopterin and methotrexate, which are inhibitors of enzymes which utilise folic acid derivatives. A newer compound of this type which showed considerable promise in clinical trials is known as CB3717 and is described and claimed in United Kingdom Patent Specification No. 2065653B. Despite its promising activity against human breast, ovarian and liver cancer, however, CB3717 shows symptoms of toxicity in humans, particularly in relation to the liver and kidney [Calvert, Alison, Harland, Robinson, Jackman, Jones, Newell, Siddik, Whiltshaw, McElwain, Smith and Harrap, *J. Clin. Oncol.*, 1986, 4, 1245; Cantwell, Earnshaw and Harris, *Cancer Treatment Reports*, 1986, 70, 1335; Bassendine, Curtin, Loose, Harris and James, *J. Hepatol.*, 1987, 4, 39; Vest, Bork and Hasen, *Eur. J. Cancer Clin. Oncol.*, 1988, 24, 201; Cantwell, Macaulay, Harris, Kaye, Smith, Milsted and Calvert, *Eur. J. Cancer Clin. Oncol.*, 1988, 24, 733; Sessa, Zucchetti, Ginier, Willems, D'Incalci and Cavalli, *Eur. J. Cancer Clin. Oncol.*, 1988, 24, 769].

Compounds of the CB3717-type are believed to act as anti-tumour agents by inhibiting the enzyme thymidylate synthase, which enzyme catalyses the methylation of deoxyuridine monophosphate to produce thymidine monophosphate which is required for DNA synthesis. The anti-tumour activity of CB3717 may be assessed *in vitro* by determining its inhibitory effect on that enzyme, and in cell cultures by its inhibitory effect on cancer cell lines such as the mouse leukaemia cell lines L1210 and L5178Y TK⁻ and the human breast cancer cell line MCF-7.

Other compounds of the CB3717-type may therefore have their anti-tumour activity assessed and compared with that of CB3717, by their activity against, for example, the same enzyme and the same cancer cell lines.

European Patent Application No. 0316657 (published 24 May 89) discloses a series of quinazoline derivatives which lack the amino acid residue of compounds of the CB3717-type. The disclosed compounds are reported to possess inhibitory activity against thymidylate synthase. Among the disclosed compounds are quinazoline derivatives wherein the amino acid residue of compounds of the CB3717-type is replaced by a residue derived from 5-aminotetrazole.

We have now found that the quinazoline derivatives of the present invention possess CB3717-type activity.

Antimetabolites, such as aminopterin and methotrexate, which are inhibitors of enzymes which utilise folic acid derivatives, have also shown promise in the treatment of various allergic diseases such as allergic rhinitis, atopic dermatitis and psoriasis. The quinazoline derivatives of the present invention, being antimetabolites of the CB3717-type, are thus of value as therapeutic agents in the treatment of, for example, allergic conditions such as psoriasis.

According to the invention there is provided a quinazoline of the formula I (set out hereinafter) wherein R¹ is hydrogen or amino, or alkyl or alkoxy each of up to 6 carbon atoms; or R¹ is alkyl of up to 3 carbon atoms which bears a hydroxy substituent, or which bears one, two or three fluoro substituents;

or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from halogeno and from alkyl and alkoxy each of up to 3 carbon atoms;

wherein R² is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, halogenoalkyl or cyanoalkyl each of up to 6 carbon atoms;

wherein Ar is phenylene or heterocyclene which may be unsubstituted or may bear one or two substituents selected from halogeno, hydroxy, amino and nitro, and from alkyl, alkoxy and halogenoalkyl each of up to 3 carbon atoms;

wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-, wherein R³ is alkyl of up to 6 carbon atoms; and

wherein Y is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; or Y is a group of the formula -A-Y¹ in which A is alkylene, cycloalkylene, alkenylene or alkynylene each of up to 6 carbon atoms, and Y¹ is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof;

wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group or an alkylimino group of up to 6 carbon atoms;

and wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy and halogeno, from alkyl, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxycarbonyl, alkanoyloxyalkyl, alkylthio, alkylsulphinyl, alkylsulphonyl, alkoxy, halogenoalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, carbamoylalkyl, N-alkylcarbamoylalkyl and N,N-dialkylcarbamoylalkyl each of up to 6 carbon atoms and from phenyl, pyridyl and phenylalkyl of up to 10 carbon atoms, and wherein each of said phenyl or phenylalkyl groups may bear a substituent selected from halogeno and nitro, and from alkyl and alkoxy each of up to 3 carbon atoms;

or a pharmaceutically-acceptable salt thereof;

provided that when R¹ is hydrogen or amino, or alkyl of up to 6 carbon atoms, and L is a group of the formula -CONH-, then Y is not tetrazolyl.

The chemical formulae referred to herein by Roman numerals are set out for convenience on a separate sheet hereinafter. In this specification the term "alkyl" includes both straight and branched alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

It will be observed that a quinazoline of the invention may possess one or more asymmetric carbon atoms e.g. when Y is a group of the formula -A-Y¹ in which A is branched-chain alkylene, and it can therefore exist in racemic and optically active forms. It is to be understood that this invention encompasses a racemic form of the quinazoline and any optically-active form thereof which possesses anti-tumour activity, it being a matter of common general knowledge how a racemic compound may be separated into its optically-active forms.

It will also be observed that a quinazoline of the invention of the formula I wherein L is a group of the formula -CH=CH- may exist as two geometric isomers. It is to be understood that this invention encompasses any geometric isomer which possesses anti-tumour activity, it being a matter of common general knowledge how geometric isomers may be separated.

Within the present invention it is to be understood that a quinazoline of the formula I may exhibit the phenomenon of tautomerism and that the formulae drawings presented within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which possesses anti-tumour activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain quinazolines of the formula I can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess anti-tumour activity.

Suitable values for the generic radicals referred to herein include those set out below.

A suitable value for R¹, R² or R³ when it is alkyl of up to 6 carbon atoms, or for an alkyl substituent of up to 6 carbon atoms which may be present as a substituent on an aryl or heteroaryl group, or a hydrogenated derivative thereof, is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl or isohexyl.

A suitable value for an alkyl substituent of up to 3 carbon atoms which may be present as a further substituent on the quinazoline ring, as a substituent on Ar, or as a substituent on a phenyl group is, for example, methyl, ethyl, propyl or isopropyl.

A suitable value for R² when it is alkenyl is, for example, prop-2-enyl, but-2-enyl, but-3-enyl or 2-methylprop-2-enyl; and when it is alkynyl is, for example prop-2-ynyl, but-2-ynyl or but-3-ynyl.

A suitable value for R¹ when it is alkoxy of up to 6 carbon atoms, or for an alkoxy substituent of up to 6 carbon atoms which may be present as a substituent on an aryl or heteroaryl group, or a hydrogenated derivative thereof, is, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy or hexyloxy.

A suitable value for an alkoxy substituent of up to 3 carbon atoms which may be present as a further substituent on the quinazoline ring, as a substituent on Ar, or as a substituent on a phenyl group is, for example, methoxy, ethoxy, propoxy or isopropoxy.

A suitable value for an alkylthio substituent of up to 6 carbon atoms which may be present as a substituent on an aryl or heteroaryl group, or a hydrogenated derivative thereof, is, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio or hexylthio.

A suitable value for a halogeno substituent which may be present as a further substituent on the quinazoline ring, as a substituent on Ar, as a substituent on an aryl or heteroaryl group, or a hydrogenated

derivative thereof, or as a substituent on a phenyl group is, for example, fluoro, chloro, bromo or iodo.

A suitable value for R¹ when it is substituted alkyl is, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

A suitable value for R¹ when it is substituted alkoxy is, for example, 2-hydroxyethoxy, 2-methoxyethoxy, 3-methoxypropoxy or 2-ethoxyethoxy.

A suitable value for R² when it is hydroxyalkyl, halogenoalkyl and cyanoalkyl is, for example, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 3-fluoropropyl, 3-chloropropyl, cyanomethyl, 2-cyanoethyl or 3-cyanopropyl.

A suitable value for Ar when it is phenylene is, for example, 1,3-phenylene or 1,4-phenylene.

A suitable value for Ar when it is heterocyclene is, for example, a 5-membered or 6-membered aromatic (that is, fully unsaturated) heterocyclene diradical which contains up to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur, for example, thienylene, pyridylene, pyrimidinylene, thiazolylene, oxazolylene or thiadiazolylene.

A suitable halogenoalkyl substituent in Ar is, for example, fluoromethyl, difluoromethyl or trifluoromethyl.

A suitable value for Y or Y¹ when it is aryl is, for example, phenyl or naphthyl which may be attached through any available position and which may bear one or two substituents.

A suitable value for Y or Y¹ when it is heteroaryl or a hydrogenated derivative thereof, is, for example, a 5-membered or 6-membered heterocyclic radical which contains up to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur, which heterocyclic radical is a single ring or is fused to a benzo ring, for example, furyl, benzofuranyl, tetrahydrofuryl, chromanyl, thienyl, pyridyl, N-oxidopyridyl, piperidiny, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoxaliny, quinazolinyl, cinnoliny, pyrrolyl, pyrrolidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl, thiadiazolyl, tetrazolyl or azepanyl, which may be attached through any available position including through any available nitrogen atom and which may bear up to three substituents including a substituent on any available nitrogen atom.

Particular values for Y and Y¹ when it is heteroaryl, or a hydrogenated derivative thereof, which bears up to three oxo substituents include for example, 1,2-dihydro-2-oxoquinoliny (especially 1,2-dihydro-2-oxoquinolin-3-yl and 1,2-dihydro-2-oxoquinolin-6-yl), 3,4-dihydro-4-oxoquinazolinyl (especially 3,4-dihydro-4-oxoquinazolin-5-yl, 3,4-dihydro-4-oxoquinazolin-6-yl, 3,4-dihydro-4-oxoquinazolin-7-yl and 3,4-dihydro-4-oxoquinazolin-8-yl), 1,2-dihydro-2-oxopyridyl (especially 1,2-dihydro-2-oxopyrid-3-yl and 1,2-dihydro-2-oxopyrid-6-yl), 3,4-dihydro-4-oxopyrimidinyl (especially 3,4-dihydro-4-oxopyrimidin-2-yl and 3,4-dihydro-4-oxopyrimidin-5-yl), 1,2,3,4-tetrahydro-2,4-dioxypyrimidinyl (especially 1,2,3,6-tetrahydro-2,6-dioxypyrimidin-4-yl and 1,2,3,4-tetrahydro-2,4-dioxypyrimidin-5-yl), 2,5-dioxopyrrolidinyl (especially 2,5-dioxopyrrolidin-3-yl), 2-oxopiperidinyl (especially 2-oxopiperidin-1-yl), 2,6-dioxopiperidinyl (especially 2,6-dioxopiperidin-3-yl) and 2-oxoazepanyl (especially hexahydro-2-oxoazepin-1-yl).

A suitable value for A when it is alkylene is, for example, methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, isopropylidene, butylidene, isobutylidene, 1-ethylethylene, 1-propylethylene, 1-isopropylethylene, tetramethylene or pentamethylene; when it is alkenylene is, for example, 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene or 3-butenylene; and when it is alkynylene is, for example, 2-propynylene, 2-butyneylene or 3-butyneylene.

A suitable value for A when it is cycloalkylene is, for example, cyclopropylidene, 1,2-cyclopropylene, cyclopentylidene, 1,2-cyclopentylene, 1,3-cyclopentylene, cyclohexylidene, 1,2-cyclohexylene or 1,4-cyclohexylene.

A suitable value for a substituent which may be present on an aryl or heteroaryl group, or a hydrogenated derivative thereof, when it is alkylamino, dialkylamino, halogenoalkyl, alkylsulphinyl or alkylsulphonyl is, for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, pentylamino, hexylamino, dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino, N-methyl-N-isopropylamino, N-ethyl-N-isopropylamino, di-isopropylamino, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, pentafluoroethyl, heptafluoropropyl, chloromethyl, dichloromethyl, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, butylsulphinyl, methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl or butylsulphonyl.

A suitable value for an alkylimino group which may replace one constituent methylene group in A is, for example, methylimino, ethylimino, propylimino or isopropylimino.

Suitable values for substituents which may be present on an aryl or heteroaryl group, or a hydrogenated derivative thereof, are, for example:-

for <u>N</u> -alkylcarbamoyl:	<u>N</u> -methylcarbamoyl, <u>N</u> -ethylcarbamoyl and <u>N</u> -propylcarbamoyl;
for <u>N,N</u> -dialkylcarbamoyl:	<u>N,N</u> -dimethylcarbamoyl;
for alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl and <u>tert</u> -butoxycarbonyl;

- for alkanoyloxyalkyl: acetoxymethyl, propionyloxymethyl, isobutyryloxymethyl and pivaloyloxymethyl;
- for hydroxyalkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
- for aminoalkyl: aminomethyl and 2-aminoethyl;
- 5 for alkylaminoalkyl: methylaminomethyl, ethylaminomethyl and 2-methylaminoethyl;
- for dialkylaminoalkyl: dimethylaminomethyl, diethylaminomethyl, 2-dimethylaminoethyl and 2-diethylaminoethyl;
- for carboxyalkyl: carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;
- for alkoxycarbonylalkyl: methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methoxycarbonyl-
10 ethyl and 2-ethoxycarbonyl-ethyl;
- for carbamoylalkyl: carbamoylmethyl, 2-carbamoyl-ethyl and 3-carbamoyl-propyl;
- for N-alkylcarbamoylalkyl: N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, 2-(N-methylcarbamoyl)-
ethyl, 2-(N-ethylcarbamoyl)-ethyl, 3-(N-methylcarbamoyl)-propyl
and 3-(N-ethylcarbamoyl)-propyl;
- 15 for N,N-dialkylcarbamoylalkyl: N,N-dimethylcarbamoylmethyl, N,N-diethylcarbamoylmethyl and 2-(N,N-dimethylcarbamoyl)-ethyl;
- for phenylalkyl: benzyl, phenethyl, phenylpropyl and phenylbutyl.

A suitable pharmaceutically-acceptable salt of a quinazoline of the invention which is sufficiently basic is an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic,
20 sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a quinazoline of the invention which is sufficiently acidic (for example a quinazoline of the invention which contains a carboxy group) is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium or tetra(2-hydroxyethyl)-
ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example
25 a salt with methylamine, trimethylamine or tris(2-hydroxyethyl)amine.

A particular quinazoline of the invention has the formula I wherein R¹ is hydrogen or amino, or is alkyl (especially methyl, ethyl and isopropyl) or alkoxy (especially methoxy and ethoxy) each of up to 6 carbon atoms; or R¹ is alkyl of up to 3 carbon atoms which bears one, two or three fluoro substituents (especially fluoromethyl, difluoromethyl, trifluoromethyl, and 2-fluoroethyl);

30 wherein the quinazoline ring may bear no further substituent or may bear one further substituent selected from halogeno (especially fluoro, chloro and bromo) and from alkyl and alkoxy each of up to 3 carbon atoms (especially methyl and methoxy);

wherein R² is alkyl (especially methyl, ethyl and propyl), alkenyl (especially prop-2-enyl), alkynyl (especially prop-2-ynyl), hydroxyalkyl (especially 2-hydroxyethyl and 3-hydroxypropyl), halogenoalkyl (especially 2-
35 fluoroethyl, 2-chloroethyl, 2-bromoethyl and 3-fluoropropyl) and cyanoalkyl (especially cyanomethyl and 2-cyanoethyl) each of up to 6 carbon atoms;

wherein Ar is phenylene (especially 1,4-phenylene) or heterocyclene (especially thienylene, pyridylene, pyrimidinylene, thiazolylene and thiadiazolylene) which is unsubstituted or which bears one or two substituents selected from halogeno (especially fluoro, chloro and bromo), hydroxy, amino and nitro, and
40 alkyl (especially methyl and ethyl), alkoxy (especially methoxy and ethoxy) and halogenoalkyl (especially fluoromethyl, difluoromethyl and trifluoromethyl) each of up to 3 carbon atoms;

wherein L is a group of the formula -CO.NH-, -CO.NR³-, -CH₂O- or -CO.O-, wherein R³ is alkyl (especially methyl and ethyl) of up to 6 carbon atoms; and

wherein Y is aryl (especially phenyl and naphthyl) each of up to 10 carbon atoms, or heteroaryl or a
45 hydrogenated derivative thereof (especially pyridyl, quinolyl, isoquinolyl, pyrimidinyl, imidazolyl, thiazolyl, 2,5-dioxopyrrolidinyl or 2,6-dioxopiperidinyl); or Y is a group of the formula -A-Y¹ in which A is alkylene (especially methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, butylidene, isobutylidene, 1-isopropylethylene and tetramethylene) of up to 6 carbon atoms, and Y¹ is aryl (especially phenyl and naphthyl) of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof (especially furyl,
50 thienyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoxaliny, quinazolinyl, cinnolinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl, tetrazolyl and hexahydro-2-oxoazepinyl);

wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group; and

55 wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy and halogeno (especially fluoro, chloro and bromo), and from alkyl (especially methyl and ethyl), alkylamino (especially methylamino and ethylamino), dialkylamino (especially dimethylamino and

diethylamino), N-alkylcarbamoyl (especially N-methylcarbamoyl and N-ethylcarbamoyl), N,N-dialkylcarbamoyl (especially N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl), alkoxycarbonyl (especially methoxycarbonyl, ethoxycarbonyl and tert-butoxycarbonyl), alkanoyloxyalkyl (especially isobutyryloxymethyl and pivaloyloxymethyl), alkylthio (especially methylthio and ethylthio), alkylsulphinyl (especially methylsulphinyl, ethylsulphinyl and isopropylsulphinyl), alkylsulphonyl (especially methylsulphonyl, ethylsulphonyl and isopropylsulphonyl), alkoxy (especially methoxy and ethoxy), halogenoalkyl (especially trifluoromethyl), carboxyalkyl (especially carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl), alkoxycarbonylalkyl (especially methoxycarbonylmethyl and 2-methoxycarbonylethyl), carbamoylalkyl (especially carbamoylmethyl and 2-carbamoylethyl), N-alkylcarbamoylalkyl (especially N-methylcarbamoylmethyl and 2-(N-methylcarbamoyl)ethyl) and N,N-dialkylcarbamoylalkyl (especially N,N-dimethylcarbamoylmethyl and 2-(N,N-dimethylcarbamoyl)ethyl) each of up to 6 carbon atoms; and from phenyl, pyridyl and phenylalkyl (especially benzyl, phenethyl and phenylpropyl) of up to 10 carbon atoms, and wherein each of said phenyl or phenylalkyl groups may bear a substituent selected from halogeno (especially fluoro, chloro and bromo) and nitro, and from alkyl (especially methyl and ethyl) and alkoxy (especially methoxy and ethoxy) each of up to 3 carbon atoms; or a pharmaceutically-acceptable salt thereof.

A further particular quinazoline of the invention has the formula I wherein R¹ is hydrogen or amino, or methyl, ethyl, methoxy or fluoromethyl; wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy; wherein R² is methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl; wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene or thiazolylene which is unsubstituted or which bears a substituent selected from fluoro, chloro, bromo, hydroxy, amino, nitro, methyl, methoxy and trifluoromethyl; wherein L is a group of the formula -CO.NH-, -CO.NR³ - or -CO.O-, wherein R³ is methyl or ethyl; and Y is phenyl, 2,5-dioxopyrrolidinyl or 2,6-dioxopiperidinyl, or Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, butylidene, isobutylidene or tetramethylene and Y¹ is phenyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, quinazolinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl or hexahydro-2-oxazepin-1-yl; wherein one constituent methylene group in A may be replaced by a thio, sulphinyl, sulphonyl or imino group; and wherein each of said phenyl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy, fluoro, chloro, bromo, methyl, ethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, isobutyryloxymethyl, pivaloyloxymethyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, methoxy, ethoxy, trifluoromethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, phenyl, pyridyl, benzyl, phenethyl or phenylpropyl, and wherein any phenyl group within said substituents may bear a substituent selected from fluoro, chloro, bromo, nitro, methyl, ethyl, methoxy and ethoxy; or a pharmaceutically-acceptable salt thereof.

A preferred quinazoline of the invention has the formula I wherein R¹ is amino, methyl, methoxy or fluoromethyl; wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy; wherein R² is methyl, ethyl, prop-2-enyl or prop-2-ynyl; wherein Ar is 1,4-phenylene, thienylene, pyridylene or thiazolylene which is unsubstituted or which bears a fluoro or nitro substituent; wherein L is a group of the formula -CO.NH- or -CO.O-; and Y is phenyl, or Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene or isobutylidene and Y¹ is phenyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-quinolyl, 4-quinolyl, 8-quinolyl, 2-pyrimidinyl, 4-pyrimidinyl, 6-quinazolinyl, 3-indolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl, 2-thiazolyl, 5-thiazolyl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl or tetrazol-5-yl, or Y is phenylsulphonyl; and wherein each of said phenyl or heteroaryl groups may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, carboxy, fluoro, chloro, methyl,

ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, pivaloyloxymethyl, methoxy, trifluoromethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, 4-pyridyl and benzyl;

or a pharmaceutically-acceptable salt thereof.

5 An especially preferred quinazoline of the invention has the formula I wherein R¹ is amino, methyl or methoxy;

wherein the quinazoline ring may bear a methyl substituent in the 7-position;

wherein R² is methyl, ethyl or prop-2-ynyl;

wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl with the group -L-Y in the 2-position, or is
10 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

wherein L is a group of the formula -CONH-;

and wherein Y is benzyl or phenylsulphonyl which may bear a nitro, cyano, carboxy or trifluoromethyl substituent, or Y is thiazol-5-ylmethyl or 1,2,3,6-tetrahydro-2,6-dioxypyrimidin-4-ylmethyl, or Y is 2,3-dihydro-4-oxoquinazolin-6-ylmethyl which may bear one or two methyl substituents;

15 or a pharmaceutically-acceptable salt thereof;

A further especially preferred quinazoline of the invention has the formula I wherein R¹ is methyl;

wherein the quinazoline ring may bear a methyl substituent in the 7-position;

wherein R² is methyl or prop-2-ynyl; wherein Ar is 1,4-phenylene, or 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

20 wherein L is a group of the formula -CO.NH-; and

Y is a group of the formula -A-Y¹ in which A is methylene and Y¹ is 2-nitrophenyl, 3-nitrophenyl, 3-cyanophenyl, 4-carboxyphenyl or 3-trifluoromethylphenyl, or Y¹ is 5-thiazolyl, 2,3-dihydro-4-oxoquinazolin-6-yl, 2,3-dihydro-2-methyl-4-oxoquinazolin-6-yl or 2,3-dihydro-2,3-dimethyl-4-oxoquinazolin-6-yl;

or a pharmaceutically-acceptable salt thereof.

25 Specific preferred quinazolines of the invention form the group of compounds:-

p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)benzamide;

p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-trifluoromethylbenzyl)-benzamide;

30 p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)benzamide;

p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-o-fluoro-N-(3-nitrobenzyl)-benzamide;

5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide;

35 p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;

p-[N-(2-amino-3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;

p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)benzamide and

40 p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-benzamide;

or a pharmaceutically-acceptable salt thereof.

According to a further feature of the present invention there is provided a quinazoline of the formula I (set out hereinafter)

wherein R¹ is alkyl or alkoxy each of up to 6 carbon atoms;

45 or R¹ is alkyl of up to 3 carbon atoms which bears a hydroxy substituent, or which bears one, two or three fluoro substituents;

or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from halogeno and from alkyl and alkoxy each of up to 3 carbon atoms;

50 wherein R² is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, halogenoalkyl or cyanoalkyl each of up to 6 carbon atoms;

wherein Ar is phenylene or heterocyclene which may be unsubstituted or may bear one or two substituents selected from halogeno, hydroxy and amino, and from alkyl, alkoxy and halogenoalkyl each of up to 3 carbon atoms;

55 wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-, wherein R³ is alkyl of up to 6 carbon atoms; and

wherein Y is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; or

Y is a group of the formula -A-Y¹ in which A is alkylene, cycloalkylene, alkenylene or alkynylene each of up

to 6 carbon atoms,

and Y¹ is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof;

wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group or an alkylimino group of up to 6 carbon atoms;

- 5 and wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy and halogeno, from alkyl, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxycarbonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, alkoxy, halogenoalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, carbamoylalkyl, N-alkylcarbamoylalkyl and N,N-dialkylcarbamoylalkyl each of up to 6 carbon atoms and from phenyl and phenylalkyl of up to 10 carbon atoms, and wherein each of said phenyl groups may bear a substituent selected from halogeno and from all and alkoxy each of up to 3 carbon atoms;
- 10 or a pharmaceutically-acceptable salt thereof;
- provided that when R¹ is all of up to 6 carbon atoms, the quinazoline ring bears no further substituents or bears one further substituent selected from halogeno and all of up to 3 carbon atoms, R² is alkyl, alkenyl or alkynyl each of up to 6 carbon atoms, Ar is phenylene which is unsubstituted or bears one or two substituents selected from halogeno, hydroxy and amino, and L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.

- A suitable value for Y or Y¹ when it is heteroaryl, or a hydrogenated derivative thereof, within the
- 20 quinazoline of the formula I as defined immediately above, is, for example, a 5-membered or 6-membered heterocyclic radical which contains up to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur, for example, furyl, benzofuranyl, tetrahydrofuryl, chromanyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl,
- 25 thiadiazolyl or tetrazolyl, which may be attached through any available position including through any available nitrogen atom and which may bear one or two substituents including a substituent on any available nitrogen atom.

- A further particular quinazoline of the invention has the formula I wherein R¹ is alkyl (especially methyl, ethyl and isopropyl) or alkoxy (especially methoxy and ethoxy) each of up to 6 carbon atoms; or R¹ is alkyl
- 30 of up to 3 carbon atoms which bears a hydroxy substituent or which bears one, two or three fluoro substituents (especially fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, hydroxymethyl and 2-hydroxyethyl); or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms (especially 2-hydroxyethoxy, 2-methoxyethoxy and 2-ethoxyethoxy);

- wherein the quinazoline ring may bear no further substituent or may bear one further substituent selected
- 35 from halogeno (especially fluoro, chloro and bromo) and from alkyl and alkoxy each of up to 3 carbon atoms (especially methyl and methoxy);

- wherein R² is hydrogen, alkyl (especially methyl, ethyl and propyl), alkenyl (especially prop-2-enyl), alkynyl (especially prop-2-ynyl), hydroxyalkyl (especially 2-hydroxyethyl and 3-hydroxypropyl), halogenoalkyl (especially 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl and 3-fluoropropyl) and cyanoalkyl (especially cyanomethyl and 2-cyanoethyl) each of up to 6 carbon atoms;
- 40

- wherein Ar is phenylene (especially 1,4-phenylene) or heterocyclene (especially thienylene, pyridylene, pyrimidinylene, thiazolylene, oxazolylene and thiadiazolylene) which is unsubstituted or which bears one or two substituents selected from halogeno (especially fluoro, chloro and bromo), hydroxy and amino and alkyl (especially methyl and ethyl), alkoxy (especially methoxy and ethoxy) and halogenoalkyl (especially fluoromethyl, difluoromethyl and trifluoromethyl) each of up to 3 carbon atoms;
- 45

wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-,

wherein R³ is alkyl (especially methyl and ethyl) of up to 6 carbon atoms; and

- wherein Y is aryl (especially phenyl and naphthyl) of up to 10 carbon atoms, or heteroaryl or a
- 50 hydrogenated derivative thereof (especially furyl, benzofuranyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl and tetrazolyl); or

- Y is a group of the formula -A-Y¹ in which A is alkylene (especially methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, 1-isopropylethylene and tetramethylene) or cycloalkylene (especially cyclopentylidene, 1,2-cyclopentylene, 1,2-cyclohexylene and 1,4-cyclohexylene) each of up to 6 carbon atoms, and Y¹ is aryl (especially phenyl and naphthyl) of up to 10 carbon atoms, or heteroaryl or a
- 55 hydrogenated derivative thereof (especially pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

thiadiazolyl and tetrazolyl); wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl or sulphonyl group; and

wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy and halogeno (especially fluoro, chloro and bromo), and from alkyl (especially methyl and ethyl), alkylamino (especially methylamino and ethylamino), dialkylamino (especially dimethylamino and diethylamino), N-alkylcarbamoyl (especially N-methylcarbamoyl and N-ethylcarbamoyl), N,N-dialkylcarbamoyl (especially N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl), alkoxycarbonyl (especially methoxycarbonyl, ethoxycarbonyl and tert-butoxycarbonyl), alkylthio (especially methylthio and ethylthio), alkylsulphinyl (especially methylsulphinyl, ethylsulphinyl and isopropylsulphinyl), alkylsulphonyl (especially methylsulphonyl, ethylsulphonyl and isopropylsulphonyl), alkoxy (especially methoxy and ethoxy), halogenoalkyl (especially trifluoromethyl), hydroxyalkyl (especially hydroxymethyl and 2-hydroxyethyl), aminoalkyl (especially aminomethyl), carboxyalkyl (especially carboxymethyl and 2-carboxyethyl), alkoxycarbonylalkyl (especially methoxycarbonylmethyl and 2-methoxycarbonyl-ethyl), carbamoylalkyl (especially carbamoylmethyl and 2-carbamoyl-ethyl), N-alkylcarbamoylalkyl (especially N-methylcarbamoylmethyl and 2-(N-methylcarbamoyl)-ethyl) and N,N-dialkylcarbamoylalkyl (especially N,N-dimethylcarbamoylmethyl and 2-(N,N-dimethylcarbamoyl)-ethyl) each of up to 6 carbon atoms; and from phenyl and phenylalkyl (especially benzyl, phenethyl and phenylpropyl) of up to 10 carbon atoms, and wherein each of said phenyl groups may bear a substituent selected from halogeno (especially fluoro, chloro and bromo) and from alkyl (especially methyl and ethyl) and alkoxy (especially methoxy and ethoxy) each of up to 3 carbon atoms; or a pharmaceutically-acceptable salt thereof.

provided that when R¹ is alkyl of up to 6 carbon atoms, the quinazoline ring bears no further substituents or bears one further substituent selected from halogeno and alkyl of up to 3 carbon atoms,

R² is alkyl, alkenyl or alkynyl each of up to 6 carbon atoms,

Ar is phenylene which is unsubstituted or bears one or two substituents selected from halogeno, hydroxy and amino, and

L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.

A further preferred quinazoline of the invention has the formula I wherein R¹ is methyl, ethyl, methoxy or fluoromethyl;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;

wherein R² is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;

wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene, thiazolylene or thiadiazolylene which is unsubstituted or which bears one or two substituents selected from fluoro, chloro, bromo, hydroxy, amino, methyl, methoxy and trifluoromethyl;

wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -CO.CH₂- or -CO.O-, wherein R³ is methyl or ethyl; and

Y is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl; or

Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, 1-isopropylethylene or tetramethylene and Y¹ is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl;

wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl or sulphonyl group; and

wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy, fluoro, chloro, bromo, methyl, ethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, isopropylsulphinyl, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, methoxy, ethoxy, trifluoromethyl, carboxymethyl, 2-carboxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, phenyl, benzyl, phenethyl or phenylpropyl, and wherein each of said phenyl groups may bear a substituent selected from fluoro, chloro, bromo, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically acceptable salt thereof;

provided that when R¹ is methyl or ethyl, the quinazoline ring bears no further substituents or bears one further substituent selected from fluoro, chloro and methyl,

R² is methyl, ethyl, propyl, prop-2-enyl or prop-2-ynyl,

Ar is 1,4-phenylene which is unsubstituted or bears one or two substituents selected from fluoro, chloro, bromo, hydroxy and amino, and

L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.

5 A further especially preferred quinazoline of the invention has the formula I wherein R¹ is methyl, ethyl, methoxy or fluoromethyl;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;

10 wherein R² is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;

wherein Ar is 1,4-phenylene, thien-2,5-diyl, pyrid-2,5-diyl or thiazol-2,5-diyl which is unsubstituted or which bears one or two substituents selected from fluoro, chloro, hydroxy, amino and methyl;

wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and

Y is phenyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl or 1,2,3-triazolyl; or

15 Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene or trimethylene and Y¹ is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl; and

wherein each of said aryl or heteroaryl groups may be unsubstituted or may bear one or two substituents selected from amino, nitro, fluoro, methyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, methylsulphonyl, methylsulphonyl, methoxy, trifluoromethyl or benzyl;

20 or a pharmaceutically acceptable salt thereof.

A further especially preferred quinazoline of the invention has the formula I wherein R¹ is methyl; wherein R² is hydrogen, methyl, ethyl, prop-2-ynyl or 2-fluoroethyl;

25 wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl or thiazol-2,5-diyl each with the group -L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-,

wherein R³ is methyl or ethyl; and

wherein Y is phenyl; or

30 Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene or trimethylene and Y¹ is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-indolyl, 3-indolyl, 1-imidazolyl, 2-imidazolyl, 2-benzimidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 3-indazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-1-yl, 2-thiadiazolyl or 5-tetrazolyl; and

35 wherein each of said aryl or heteroaryl groups may be unsubstituted or may bear one or two substituents selected from amino, nitro, carbamoyl, fluoro, methyl, ethoxycarbonyl, methylsulphonyl, methylsulphonyl, methoxy, trifluoromethyl or benzyl;

or a pharmaceutically-acceptable salt thereof.

A further especially preferred quinazoline of the invention has the formula I wherein R¹ is methyl; wherein R² is methyl, ethyl or prop-2-ynyl; wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl or thiazol-2,5-diyl each with the group -L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

wherein L is a group of the formula -CO.NH- and

Y is a group of the formula -A-Y¹ in which A is methylene or ethylene and Y¹ is 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-indolyl or 1,2,4-triazol-1-yl, or Y¹ is phenyl which may be unsubstituted or may bear a substituent

45 selected from amino, nitro, ethoxycarbonyl or trifluoromethyl;

or a pharmaceutically-acceptable salt thereof.

Further specific preferred quinazolines of the invention form the group of compounds:-

N-benzyl-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamide;

p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)benzamide;

50 p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-methyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylmethyl)benzamide;

p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)benzamide

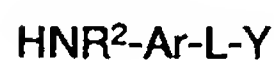
and

N-benzylimidazol-2-ylmethyl p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]benzoate.

55 A quinazoline of the invention, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds.

Such processes are provided as a further feature of the invention and are illustrated by the following representative examples, processes (a) to (f).

(a) A preferred process for the manufacture of a quinazoline of the invention comprises the reaction of a compound of the formula II (set out hereinafter) wherein R^1 has the meaning stated above, provided that when R^1 is amino, hydroxyalkyl or hydroxyalkoxy any amino or hydroxy group is protected by a conventional protecting group, R^4 is hydrogen or a protecting group and Z is a displaceable group, with a compound of the formula:-



wherein R^2 , Ar, L and Y have the meanings stated above, provided that when there is an amino, alkylamino, imino, hydroxy or carboxy group in R^2 , Ar or Y, any amino, alkylamino, imino and carboxy group is protected by a conventional protecting group and any hydroxy group may be protected by a conventional protecting group or alternatively any hydroxy group need not be protected; whereafter any undesired protecting group in R^1 , R^2 , Ar and Y is removed.

The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an organic amine base such as, for example, pyridine, lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is preferably carried out in a suitable inert solution or diluent, for example dimethylformamide, dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide and at a temperature in the range, for example, 25 to 150 °C, conveniently at or near 80 °C.

A suitable protecting group for a hydroxy group may be, for example, an esterifying group, for example an acetyl or benzoyl group, which may be removed by hydrolysis with a base, for example sodium hydroxide, or provided that R^2 , L and Y do not contain an alkenyl or alkynyl group, the protecting group may be, for example, an α -arylalkyl group, for example a benzyl group, which may be removed by hydrogenation over a catalyst, for example palladium-on-charcoal.

A suitable protecting group for an amino, alkylamino or imino group may be, for example, an alkoxy carbonyl group, for example a tert-butoxycarbonyl group which may be removed by treatment with an organic acid, for example trifluoroacetic acid; or it may be, for example, a benzyloxycarbonyl group which may be removed by treatment with a Lewis acid, for example boron tris(trifluoroacetate).

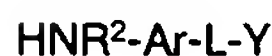
A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a carboxy group may be an esterifying group, for example a methyl or an ethyl group which may be removed by hydrolysis with a base, for example sodium hydroxide; or, for example a tert-butyl group which may be removed by treatment with an organic acid, for example trifluoroacetic acid.

A suitable value for R^4 when it is a protecting group is, for example, a pivaloyloxymethyl group which may be removed by hydrolysis with a base, for example sodium hydroxide.

Z may be, for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-p-sulphonyloxy group.

The compound of the formula:-

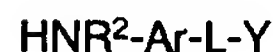


wherein L is a group of the formula -CONH- or -CONR³- wherein R^3 has the meanings stated above, used as a starting material above, may be obtained by the reaction of an acid of the formula $\text{O}_2\text{N-Ar-CO}_2\text{H}$, or a reactive derivative thereof, wherein Ar has the meaning stated above with an amine of the formula $\text{H}_2\text{N-Y}$ or $\text{R}^3\text{NH-Y}$ wherein R^3 and Y have the meanings stated above and any amino, alkylamino, imino and carboxy group in Ar and Y is protected by a conventional protecting group as stated above and any hydroxy group in Ar and Y may be protected by a conventional protecting group as stated above or alternatively any hydroxy group need not be protected. Thereafter the nitro group may be reduced by conventional means to an amino group which in turn may be alkylated with a compound of the formula $\text{R}^2\text{-Z}$ wherein R^2 and Z have the meanings stated above.

A suitable reactive derivative of an acid of the formula given above may be, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by

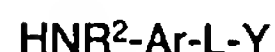
the reaction of the acid and a phenol such as pentafluorophenol; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide, for example dicyclohexylcarbodiimide.

5 The compound of the formula:-



10 wherein L is a group of the formula $-\text{NH.CO}-$ or $-\text{NR}^3.\text{CO}-$ wherein R^3 has the meaning stated above, used as a starting material above, may be obtained by the reaction of an amine of the formula $\text{HNR}^2\text{-Ar-NH}_2$, wherein Ar has the meaning stated above with an acid of the formula $\text{HO}_2\text{C-Y}$, or a reactive derivative thereof, wherein Y has the meaning stated above and any amino, alkylamino, imino and carboxy group in Ar and Y is protected by a conventional protecting group as stated above and any hydroxy group in Ar and Y may be protected by a conventional protecting group as stated above or
15 alternatively any hydroxy group need not be protected.

The compound of the formula:-



20 wherein L is a group of the formula $-\text{CH}=\text{CH}-$, used as a starting material above, may be obtained by the reaction of an aldehyde of the formula $\text{HNG}^1\text{-Ar-CHO}$ wherein Ar has the meaning stated above and G^1 is a conventional protecting group for an amino group as stated above, for example an alkoxycarbonyl group, with a triphenylphosphonium salt of the formula:-



wherein Y has the meaning stated above and wherein Z^- is an anion, for example the bromide ion, and any amino, alkylamino and imino group in Ar and Y is protected by a conventional protecting group as stated above and any hydroxy and carboxy group in Ar and Y may be protected by a conventional
30 protecting group as stated above or alternatively any hydroxy and carboxy group need not be protected.

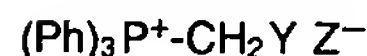
The reaction may be carried out in solution in dimethyl sulphoxide in the presence of dimethyl sodium. Thereafter the protecting group G^1 may be removed by conventional means and whereafter the amine of the formula:-



may be alkylated with a compound of the formula $\text{R}^2\text{-Z}$ wherein R^2 and Z have the meanings stated above.

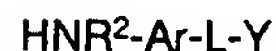
The protecting group G^1 may be chosen such that it may be removed while the conventional
40 protecting group on any amino, alkylamino and imino group in Ar and Y remains intact.

The triphenylphosphonium salt of the formula:-

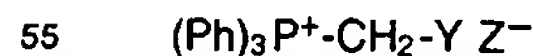


45 used as a starting material above may be obtained by the reaction of triphenylphosphine with a compound of the formula $\text{Y-CH}_2\text{-Z}$ wherein Y and Z have the meanings stated above.

Alternatively the compound of the formula:-



50 wherein L is a group of the formula $-\text{CH}=\text{CH}-$, used as a starting material above, may be obtained by the reaction of an aldehyde of the formula $\text{O}_2\text{N-Ar-CHO}$ wherein Ar has the meaning stated above with a triphenylphosphonium salt of the formula:-

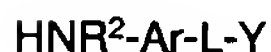


wherein Y and Z^- have the meanings stated above and any amino, alkylamino and imino group in Ar and Y is protected by a conventional protecting group as stated above and any hydroxy and carboxy group

in Ar and Y may be protected by a conventional protecting group as stated above or alternatively any hydroxy and carboxy group need not be protected.

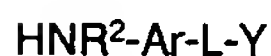
The reaction may be carried out in solution in dimethylsulphoxide in the presence of dimethyl sodium. Thereafter the nitro group may be reduced by conventional means to an amino group which in turn may be alkylated with a compound of the formula R^2-Z wherein R^2 and Z have the meanings stated above.

The compound of the formula:-



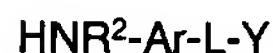
wherein L is a group of the formula $-CH_2O-$, used as a starting material above, may be obtained by the reaction of an alcohol of the formula $O_2N-Ar-CH_2OH$ wherein Ar has the meaning stated above with a compound of the formula Y-Z wherein Y and Z have the meanings stated above and any amino, alkylamino, imino, hydroxy and carboxy group in Ar and Y is protected by a conventional protecting group as stated above, whereafter the nitro group may be reduced by conventional means to an amino group which may in turn be alkylated with a compound of the formula R^2-Z wherein R^2 and Z have the meanings stated above.

The compound of the formula:-



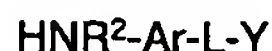
wherein L is a group of the formula $-CH_2S-$, used as a starting material above, may be obtained by the reaction of a thiol of the formula $O_2N-Ar-CH_2SH$ wherein Ar has the meaning stated above with a compound of the formula Y-Z wherein Y and Z have the meanings stated above and any amino, alkylamino, imino and carboxy group in Ar and Y is protected by a conventional protecting group as stated above and any hydroxy group in Ar and Y may be protected by a conventional protecting group as stated above or alternatively any hydroxy group need not be protected. Thereafter the nitro group may be reduced by conventional means to an amino group which in turn may be alkylated with a compound of the formula R^2-Z wherein R^2 and Z have the meanings stated above.

The compound of the formula:-



wherein L is a group of the formula $-OCH_2-$ or $-SCH_2-$, used as a starting material above, may be obtained by the reaction of a compound of the formula $O_2N-Ar-OH$ or $O_2N-Ar-SH$ wherein Ar has the meaning stated above with a compound of the formula Y- CH_2 -Z wherein Y and Z have the meanings stated above and any amino, alkylamino, imino and carboxy group in Ar and Y is protected by a conventional protecting group as stated above, any hydroxy group in Ar is protected by a conventional protecting group as stated above, and any hydroxy group in Y may be protected by a conventional protecting group as stated above or alternatively any hydroxy group in Y need not be protected. Thereafter the nitro group may be reduced by conventional means to an amino group which in turn may be alkylated with a compound of the formula R^2-Z wherein R^2 and Z have the meanings stated above.

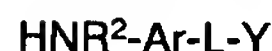
The compound of the formula:-



wherein L is a group of the formula $-CO.CH_2-$ used as a starting material above, may be obtained by the reaction of an organometallic compound of the formula $M-NG^1-Ar-C(OM)=CH_2$ wherein G^1 and Ar have the meanings stated above and M is a metal group, for example lithium, with a compound of the formula Y-Z, wherein Y and Z have the meanings stated above and any amino, alkylamino, imino, hydroxy and carboxy group in Ar and Y is protected by conventional protecting group as stated above, and thereafter with water. Thereafter the protecting group G^1 may be removed by conventional means while the conventional protecting group on any amino, alkylamino and imino group in Ar and Y remains intact whereafter the amine may be alkylated with a compound of the formula R^2-Z wherein R^2 and Z have the meanings stated above.

The organometallic compound of the formula $M-NG^1-Ar-C(OM)=CH_2$ used as a starting material above may be obtained by the reaction of the ketone of the formula $NHG^1-Ar-CO.CH_3$ with a metal amide, for example a lithium amide, for example lithium diisopropylamide, in a conventional solvent, for example tetrahydrofuran.

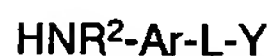
The compound of the formula:-



5 wherein L is a group of the formula $-\text{CH}_2\text{.CO-}$, used as a starting material above, may be obtained by the reaction of an acid of the formula $\text{HNG}^1\text{-Ar-CH}_2\text{.CO}_2\text{H}$, or a reactive derivative thereof, wherein G^1 and Ar have the meanings stated above with an organometallic compound of the formula Y-M wherein Y has the meaning stated above and M is a metal group, for example magnesium or cadmium, and any amino, alkylamino, imino, hydroxy and carboxy group in Ar and Y is protected by a conventional protecting group as stated above, whereafter the protecting group G^1 may be removed by conventional means while the conventional protecting group on any amino, alkylamino and imino group in Ar and Y remains intact and whereafter the amine may be alkylated with a compound of the formula $\text{R}^2\text{-Z}$ wherein R^2 and Z have the meanings stated above.

The compound of the formula:-

15



20 wherein L is a group of the formula $-\text{CO.O-}$, used as a starting material above, may be obtained by the reaction of an acid of the formula $\text{O}_2\text{N-Ar-CO}_2\text{H}$, or a conventional reactive derivative thereof, wherein Ar has the meaning stated above with an alcohol of the formula HO-Y wherein Y has the meaning stated above and any amino, alkylamino, imino, hydroxy and carboxy group in Ar and Y is protected by a conventional protecting group. Thereafter the nitro group may be reduced by conventional means to an amino group which in turn may be alkylated with a compound of the formula $\text{R}^2\text{-Z}$ wherein R^2 and Z have the meanings stated above.

25 (b) A further preferred process for the manufacture of a quinazoline of the invention wherein L is a group of the formula $-\text{CONH-}$ or $-\text{CONR}^3\text{-}$, comprises the reaction of an acid of the formula III, or a reactive derivative thereof, with a compound of the formula $\text{H}_2\text{N-Y}$ or $\text{R}^3\text{NH-Y}$ wherein R^1 , R^2 , R^3 , R^4 , Ar and Y have the meanings stated above and any amino, alkylamino, imino and carboxy group in R^1 , Ar and Y is protected by a conventional protecting group as stated above and any hydroxy group in R^1 , R^2 , Ar and Y may be protected by a conventional protecting group as stated above or alternatively any hydroxy group need not be protected; whereafter the protecting groups are removed by conventional means.

30 A suitable reactive derivative of an acid of the formula given above may be, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide, for example dicyclohexylcarbodiimide.

40 The reaction is preferably carried out in the presence of a suitable base as stated above, in a suitable solvent or diluent such as methylene chloride, dimethylformamide, dimethylacetamide or dimethylsulphoxide and at a temperature in the range, for example, 10 to 100 °C, conveniently at or near laboratory temperature.

45 The carboxylic acid used as starting material may be obtained by the reaction of a compound of the formula II wherein R^1 , R^4 and Z have the meanings stated above, with a compound of the formula:



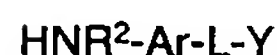
50 wherein R^2 and Ar have the meanings stated above and R^5 is a protecting group which can be removed to provide a carboxylic acid. R^5 may be, for example, a methyl or an ethyl group which may be removed by hydrolysis with a base, for example sodium hydroxide or R^5 may be, for example, a tert-butyl group which may be removed by cleavage with an organic acid, for example trifluoroacetic acid. The protecting group for the carboxy group in R^5 may be, for example, an esterifying group which can be removed while the protecting group for any amino, alkylamino, imino, carboxy and hydroxy group in R^1 , R^2 , Ar and Y is retained.

55 (c) A further preferred process for the manufacture of a quinazoline of the invention wherein L is a group of the formula $-\text{CO.O-}$, comprises the reaction, in the presence of a suitable base as stated above, of an acid of the formula III, or a reactive derivative thereof,

with a compound of the formula HO-Y, wherein R¹, R², R³, R⁴, Ar and Y have the meanings stated above and any amino, alkylamino, imino, hydroxy and carboxy group in R¹, R², Ar and Y is protected by a conventional protecting group as stated above; whereafter the protecting groups are removed by conventional means.

5 The reaction is preferably carried out in a suitable solvent or diluent such as dimethylformamide, dimethylacetamide or dimethylsulphoxide at a temperature in the range 10 to 100 °C, conveniently at or near laboratory temperature.

(d) A further preferred process for the manufacture of a quinazoline of the invention, wherein R¹ is alkoxy, hydroxyalkoxy or alkoxyalkoxy, comprises the reaction of a compound of the formula IV wherein
10 R¹ has the last-mentioned meaning stated above, provided that when there is a hydroxy substituent in R¹ it is protected by a conventional protecting group as stated above, and Z is a displaceable group, with a compound of the formula:



15 wherein R², Ar, L and Y have the meanings stated above, provided that when there is an amino, alkylamino, imino, hydroxy or carboxy group in R², Ar or Y any amino, alkylamino, imino and carboxy group is protected by a conventional protecting group as stated above and any hydroxy group may be protected by a conventional protecting group, as stated above or alternatively any hydroxy group need
20 not be protected;

whereafter the protecting groups are removed by conventional means, as stated above and the R¹ group situated at the 4-position of the quinazoline ring is cleaved by hydrolysis with a base, for example sodium hydroxide, to form a quinazoline of the invention.

(e) A further preferred process for the manufacture of a quinazoline of the invention wherein Y is a group of the formula -A-Y¹ in which one constituent methylene group in A is replaced by a sulphinyl or sulphonyl group, or wherein there is an alkylsulphinyl or alkylsulphonyl substituent in Y, comprises the
25 oxidation of a compound of the formula I wherein Y is a group of the formula -A-Y¹ in which A is replaced by a thio group, or wherein there is an alkylthio substituent in Y, with a suitable oxidising agent.

A suitable oxidising agent is, for example, any reagent known to oxidise a thio group to a sulphinyl or sulphonyl group, for example, hydrogen peroxide, a peracid such as 3-chloroperbenzoic acid or peroxyacetic acid, or chromium trioxide. When a compound carrying a sulphinyl group is required the required stoichiometric amount of any one of the above oxidising agents may be used in order to reduce the production of a compound carrying a sulphonyl group. Alternatively a milder oxidising agent may be used, for example sodium or potassium metaperiodate. It will be appreciated that when a compound of
30 the formula I containing a sulphonyl group is required, it may be obtained by the oxidation of the corresponding sulphinyl compound as well as by the oxidation of the corresponding thio compound.

(f) A further preferred process for the manufacture of a quinazoline of the invention wherein there is a carboxy or carboxyalkyl substituent in Y, comprises the cleavage of a compound of the formula I wherein there is an alkoxycarbonyl or alkoxycarbonylalkyl substituent in Y.

40 Suitable conditions for the cleavage reaction include, for example, hydrolysis with a base, for example sodium hydroxide; or when, for example, a tert-butyl group is to be cleaved, treatment with an organic acid, for example trifluoroacetic acid.

When a pharmaceutically-acceptable salt of a novel compound of the formula I is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional
45 procedure. When an optically active form of a compound of the formula I is required, it may be obtained by carrying out one of the aforesaid processes using an optically active starting material, or by resolution of a racemic form of said compound using a conventional procedure.

As stated above a quinazoline derivative of the present invention possesses anti-tumour activity. This activity may be assessed, for example, using one or more of the procedures set out below:-

50 (a) An in vitro assay which determines the ability of a test compound to inhibit the enzyme thymidylate synthase. Thymidylate synthase was obtained in partially purified form from L1210 mouse leukaemia cells and utilised using the procedures described by Jackman et al. (Cancer Res., 1986, 46, 2810);

(b) An assay which determines the ability of a test compound to inhibit the growth of the leukaemia cell line L1210 in cell culture. The test is similar to that described in UK Patent Specification No. 2065653B;

55 (c) An assay which determines the ability of a test compound to inhibit the growth of the human breast cancer cell line MCF-7 in cell culture. The test is similar to that described by Lippman et al. (Cancer Res., 1976, 36, 4595); and

(d) An assay which determines the ability of a test compound to inhibit the growth of the lymphoma cell line L5178Y TK-/- in vitro. The lymphoma cell line L5178Y TK-/- is deficient in the enzyme thymidine kinase which enzyme phosphorylates thymidine and thus operates to generate a pool of thymidylate when de novo synthesis of thymidylate is prevented by the presence of an effective amount of an inhibitor of thymidylate synthase. The L5178Y TK-/- cell line is thereby more sensitive to the presence of an inhibitor of thymidylate synthase. [L5178Y TK-/- was obtained by mutation of the parent L5178Y cell line which is described by, for example, Fischer et al., Methods in Medical Research, 1964, 10, 247]. The assay utilises a double layer soft-agar cloning technique similar to that described by Courtenay et al. (British J. Cancer, 1976, 34, 39). Each test compound is added at a range of concentrations to L5178Y TK-/- cells which have entered exponential growth phase in cell culture and the cells are incubated for 18 hours, harvested, washed with fresh culture medium and plated into soft-agar for clonogenic evaluation. After about 12 days colonies of cells are stained and counted.

A quinazoline of the present invention may itself be active or it may be a pro-drug which is converted in vivo to an active compound.

Although the pharmacological properties of the quinazolines of the invention vary with structural changes, in general quinazolines of the invention possess activity in one or more of the above tests (a) to (d):-

Test (a) IC_{50} in the range, for example, 0.02-10 μM ;

Test (b) IC_{50} in the range, for example, 0.5-100 μM ;

Test (c) IC_{50} in the range, for example, 0.1-100 μM ;

Test (d) The dose required to reduce the fraction of surviving cells to 10% of those treated lies in the range, for example, 1-100 μM .

In general those quinazolines of the invention which are particularly preferred possess activity in one or more of the above tests (a) to (d):-

Test (a) IC_{50} in the range, for example, 0.02-1 μM ;

Test (b) IC_{50} in the range, for example, 0.5-10 μM ;

Test (c) IC_{50} in the range, for example, 0.1-5 μM ;

Test (d) The dose required to reduce the fraction of surviving cells to 10% of those treated lies in the range, for example, 1-50 μM .

Thus, by way of example, the quinazoline, p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylmethyl)benzamide has an IC_{50} of 0.5 μM against thymidylate synthase [Test (a)] and IC_{50} of 3.9 μM against the L1210 cell line [Test (b)]; and the quinazoline, p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)benzamide has IC_{50} of 0.05 μM in Test (a) and an IC_{50} of 1.8 μM in Test (b).

A quinazoline of the invention, or a pharmaceutically-acceptable salt thereof, may be administered to a warm-blooded animal, including a human, in the form of a pharmaceutical composition which comprises the quinazoline, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, as a tablet or capsule, or, especially for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), as a sterile solution, suspension or emulsion, or for topical administration, as an ointment or cream, or for rectal administration as a suppository.

The composition may contain, in addition to the quinazoline of the invention, one or more other anti-tumour substances selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; other antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide and biological response modifiers, for example interferon.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The quinazoline will normally be administered to a warm-blooded animal at a unit dose within the range 50-5000 mg per square metre body area of the animal, i.e. approximately 1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example, 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage will be determined by the practitioner who is treating any particular patient.

According to further feature of the present invention there is provided a method for producing an anti-tumour effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline of the present invention, or a pharmaceutically-acceptable salt thereof. The invention also provides the use of a quinazoline of the present invention, or a pharmaceutically-acceptable salt thereof, in the manufacture of a novel medicament for use in the production of an anti-tumour effect in a warm blooded animal, such as man.

A quinazoline of the present invention is expected to possess a wide range of anti-tumour activities. CB3717 showed promising activity against human breast, ovarian and liver cancer and consequently it is expected that a quinazoline of the present invention will possess anti-tumour activity against these cancers. It is in addition expected that a quinazoline of the present invention will possess anti-tumour activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas. Such tumours require thymidine monophosphate as one of the essential nucleotides for the synthesis of cellular DNA. In the presence of an effective amount of a thymidylate synthase inhibitor such as an effective amount of a quinazoline of the present invention it is expected that tumour growth will be inhibited.

As previously mentioned a quinazoline of the invention, or a pharmaceutically-acceptable salt thereof, is also of value in the treatment of, for example, allergic conditions such as psoriasis. In using a quinazoline of the invention for this purpose the compound will normally be administered at a dose within the range 50-5000 mg per square metre body area of the animal. In general for the treatment of an allergic condition such as psoriasis topical administration of a quinazoline of the invention is preferred. Thus, for example, for topical administration a daily dose in the range, for example, 1 to 50 mg/kg will be used.

The invention is illustrated but not limited by the following Examples in which unless otherwise stated:-

- (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;
- (ii) operations were carried out at laboratory temperature, that is in the range 18-20 °C and under an atmosphere of an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) obtained from E. Meck, Darmstadt, W. Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the end-products of the formula I have satisfactory microanalyses and their structures were confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were determined using a Jeol FX 90Q or a Bruker AM200 spectrometer operating at a field strength of 200 MHz; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; d of d's, doublet of doublet's; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were obtained using a VG Analytical MS9 spectrometer and xenon gas and, where appropriate, either positive ion data or negative ion data were collected];
- (vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis; and
- (vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, a Koffler hot plate apparatus or an oil-bath apparatus.

EXAMPLE 1

Diphenylphosphoryl azide (0.7 ml) and triethylamine (1.1 ml) were added successively to a mixture of p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (as its trifluoroacetic acid salt; 1.0 g; UK Patent Specification No. 2188319A) and dimethylsulphoxide (40 ml) and the mixture was stirred at laboratory temperature for 5 hours. 3-Aminomethylpyridine (0.33 ml) was added and the mixture was stirred at laboratory temperature for 16 hours. The mixture was poured onto a mixture of ice and water (200 ml). The solid so obtained was filtered off, washed with water (3 x 30 ml) and dried; resuspended in ethyl acetate, triturated, filtered off and dried. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)benzamide (containing one equivalent of water, 0.82 g), m.p. 237-239 °C.

NMR Spectrum: (CD_3SOCD_3) 2.33 (s, 3H, 2- CH_3), 3.19 (t, 1H, $\text{C}\equiv\text{CH}$, $J=2$ Hz), 4.31 (d, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$, $J=2$ Hz), 4.45 (d, 2H, NHCH_2 , $J=6$ Hz), 4.78 (s, 2H, CH_2N), 6.84 (d, 2H, aromatic, $J=9$ Hz), 7.32 (d of d's, 1H, pyridine ring, $J=6$ and 3 Hz), 7.52 (d, 1H, 8-H, $J=8$ Hz), 7.69 (d of d's, 1H, 7-H, $J=8$ and 2 Hz), 7.70 (d of d's, 1H, pyridine ring, $J=6$ and 1.5 Hz), 7.74 (d, 2H, aromatic, $J=9$ Hz), 7.97 (d, 1H, 5-H, $J=2$ Hz), 8.42 (d of d's, 1H, pyridine ring, $J=3$ and 1.5 Hz), 8.51 (d, 1H, pyridine ring, $J=1.5$ Hz), 8.72 (t, 1H, CONH,

EP 0 373 891 B1

J = 6 Hz);

Mass Spectrum: (positive ion FAB) m/e (P + 1) 438;

5

Elemental Analysis: Found	C, 68.4;	H, 5.5;	N, 15.3;
C ₂₆ H ₂₃ N ₅ O ₂ · 1H ₂ O requires	C, 68.6;	H, 5.5;	N, 15.4%.

EXAMPLE 2

10

The process described in Example 1 was repeated using, where necessary, the appropriate benzoic acid in place of p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino] benzoic acid and the appropriate amine, or the appropriate alcohol, in place of 3-aminomethylpyridine. There were thus obtained the compounds described in the following tables, the structures of which were confirmed by proton

15 magnetic resonance and mass spectroscopy and by elemental analysis.

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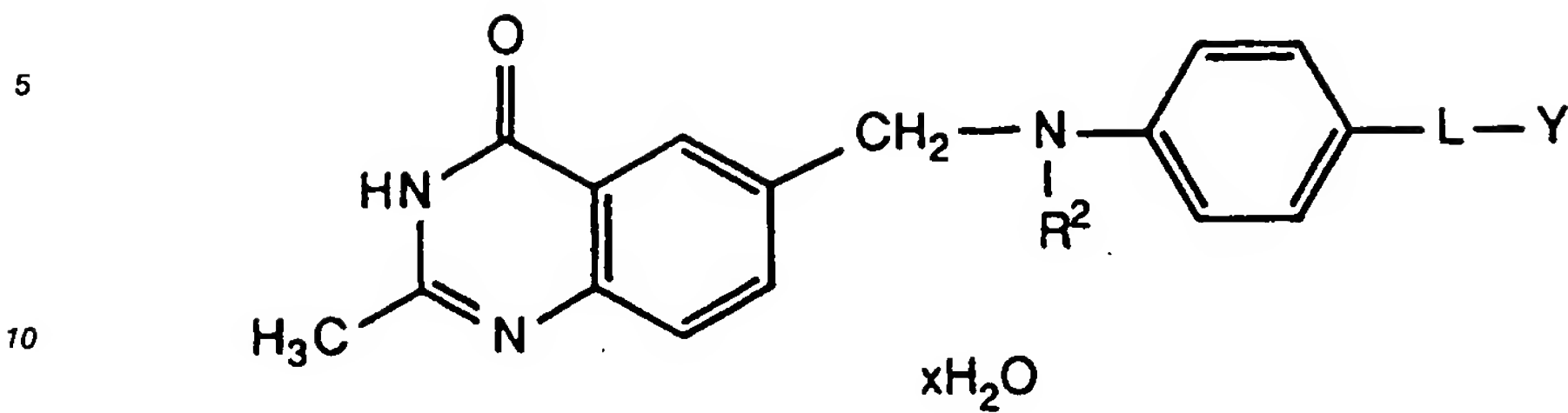
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TABLE I



15

Compound No.	R^2	L	Y	x	m.p. ($^{\circ}\text{C}$)
(Note)					
20 1	prop-2-ynyl	-CONH-	2-pyridylmethyl	1	212-218 (decomp.)
25 2	prop-2-ynyl	-CONH-	4-pyridylmethyl	1	243-244 (decomp.)
30 3	prop-2-ynyl	-CONH-	2-(pyrid-2-yl)-ethyl	1	219-221
35 4(1)	prop-2-ynyl	-CONH-	1-(pyrid-3-yl)-ethyl	1	203-209
40 5(2)	prop-2-ynyl	-CONH-	(1-benzylimidazol-2-yl)methyl	0.5	234-237
45 6(3)	ethyl*	-CONH-	(1-methylimidazol-2-yl)methyl	0.3	295-300
50 7	ethyl*	-CONH-	2-(imidazol-4-yl)-ethyl	0.5	197-205

5	Compound	R ²	L	Y	x	m.p.
	No.					(°C)
	(Note)					
10	8	ethyl*	-CONH-	3-(imidazol-1-yl)- propyl	2	138-142
15	9(4)	ethyl*	-CO.O-	(1-benzylimidazol- 2-yl)methyl	0.5	166-169
20	10(5)	ethyl*	-CO.O-	(1-methylimidazol- 2-yl)methyl	0.5	110-118
25	11(6)	prop-2-ynyl	-CONH-	5-tetrazolylmethyl	1.3	257-260 (decomp.)
30	12(7)	prop-2-ynyl	-CONH-	(1-methyltetrazol- 5-yl)methyl	1.8	251-255
35	13(8)	prop-2-ynyl	-CONH-	3-(tetrazol-5-yl)- propyl	3	239-243
40	14	ethyl*	-CONH-	2-benzimidazolyl- methyl	2	176-181
40	15	ethyl*	-CONH-	2-(indol-3-yl)- ethyl	0.5	220-223

45 **NOTES**

* p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]benzoic acid (as its trifluoroacetic acid salt) was obtained by the same method described in UK Patent Specification No. 2188319A for the preparation of p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (as its trifluoroacetic acid salt) except that ethyl iodide was used in place of propargyl bromide.

(1) The appropriate amine is described in J. Heterocyclic Chem., 1968, 5, 715.

(2) The appropriate amine was prepared as follows:-

A solution of 1-benzyl-2-chloromethylimidazole (5.5 g; J. Amer. Chem. Soc., 1949, 71, 383) in dimethylformamide (10 ml) was added dropwise to a solution of potassium phthalimide (5.7 g) in dimethylformamide (15 ml) and the mixture was stirred at laboratory temperature for 18 hours. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in chloroform (200 ml) and washed with a 0.2N aqueous solution of sodium hydroxide and then with water. The organic solution was dried (MgSO₄) and evaporated and the residue was purified by chromatography on a silica gel

column using ethyl acetate as eluent. There was thus obtained as an oil, which solidified on standing, 1-benzyl-2-phthalimidomethylimidazole (3.1 g), m.p. 148-151 °C.

Hydrazine hydrate (0.4 ml of an 85% solution in water) was added to a solution of the product so obtained (2.2 g) in methanol (50 ml) and the mixture was heated to reflux for 1 hour. The mixture was evaporated and the residue was purified by chromatography on a silica gel column using a 92:5:3 v/v mixture of ethyl acetate, methanol and an aqueous solution of ammonium hydroxide (30% by weight of NH₃) as eluent. There was thus obtained as a yellow liquid 2-aminomethyl-1-benzylimidazole (1.2 g), the structure of which was confirmed by proton magnetic resonance and mass spectroscopy.

(3) The appropriate amine was prepared as follows:-

A mixture of 2-chloromethyl-1-methylimidazole hydrochloride (2.9 g; obtained using a similar method to that described in J. Amer. Chem. Soc., 1949, 71, 383 for the preparation of 1-benzyl-2-chloromethylimidazole) and liquid ammonia (12 ml) was allowed to stand at laboratory temperature for 2 hours and then heated to reflux for 2 hours. The excess of ammonia was then evaporated. The residue was dissolved in chloroform, the solution was filtered and the filtrate was evaporated. There was thus obtained as a yellow solid 2-aminomethyl-1-methylimidazole (1.3 g) which was used without further purification.

(4) The appropriate alcohol, 1-benzyl-2-hydroxymethylimidazole is described in J. Amer. Chem. Soc., 1949, 71, 383.

(5) The appropriate alcohol was obtained using a similar method to that described in J. Amer. Chem. Soc., 1949, 71, 383 for the preparation of 1-benzyl-2-hydroxymethylimidazole.

(6) The appropriate amine is described in J. Org. Chem., 1959, 24, 1643.

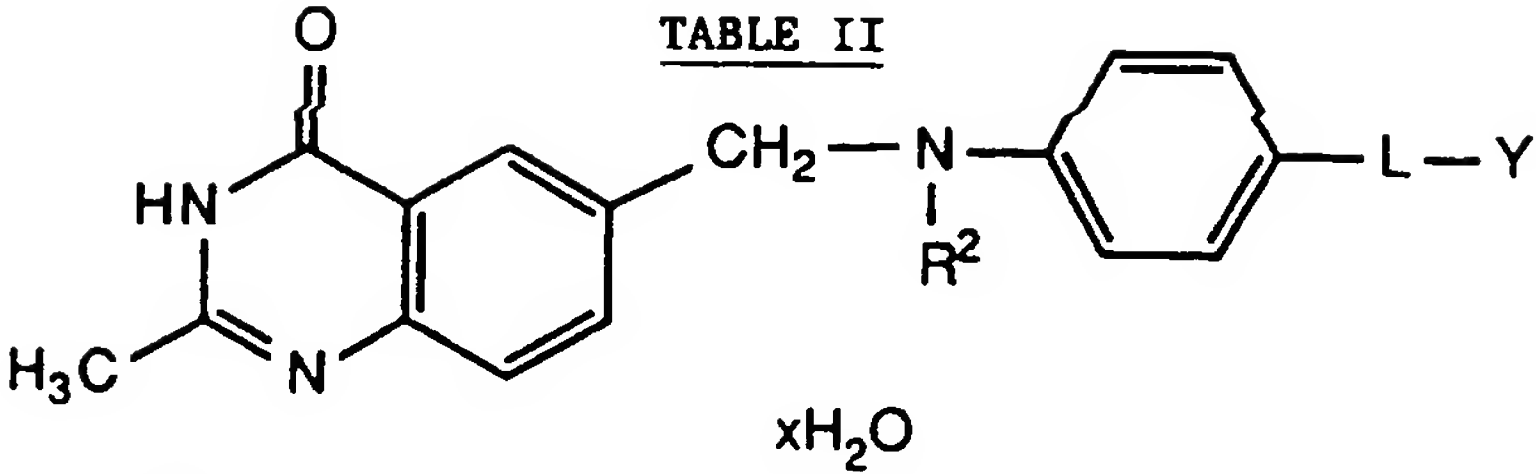
(7) The appropriate amine was prepared as follows:-

A mixture of 5-phthalimidomethyltetrazole (5 g; J. Org. Chem., 1959, 24, 1643), bis(tributyltin) oxide (11 ml) and methyl iodide (9 ml) was stirred vigorously at laboratory temperature for 3 days. The mixture was evaporated to dryness and the residue was washed with hexane and then triturated under ethanol. There was thus obtained as a white solid 1-methyl-5-phthalimidomethyltetrazole (3.1 g).

A mixture of the product so obtained (1.5 g), hydrazine hydrate (0.3 ml of an 85% solution in water) and ethanol (25 ml) was heated to reflux for 3 hours. The mixture was cooled in ice, filtered and evaporated. There was thus obtained 2-aminomethyl-1-methyltetrazole as an oil (0.3 g) which was stored at 4 °C and used without further purification.

(8) The appropriate amine was obtained using the method described in J. Org. Chem., 1959, 24, 1643 and using 4-aminobutyronitrile in place of aminoacetonitrile.

TABLE II



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Compound No. (Note)	R^2	L	Y	x	m.p. (°C)
1(1)	prop-2-ynyl	-CONH-	phenyl	0.8	262-266
2(2)	prop-2-ynyl	-CONH-	4- <u>tert</u> -butoxy-carbonylphenyl		211-214 (decomp.)
3(3)	prop-2-ynyl	-CONH-	4-carboxyphenyl	0.8	283-292 (decomp.)
4	prop-2-ynyl	-CONH-	benzyl	0.8	231-234
5	prop-2-ynyl	-CONH-	[S](-)- α -methylbenzyl		200-205
6	prop-2-ynyl	-CONH-	[R](+)- α -methylbenzyl	0.8	214-216
7	prop-2-ynyl	-CONH-	4-chlorobenzyl	0.8	226-230
8	prop-2-ynyl	-CONH-	3-chlorobenzyl	1	195-198
9	prop-2-ynyl	-CONH-	2-chlorobenzyl	0.3	205-210

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5	Compound	R ²	L	Y	x	m.p.
	No.					(°C)
	(Note)					
10	10	prop-2-ynyl	-CONH-	4-nitrobenzyl	2	229-233
	11	prop-2-ynyl	-CONH-	3-nitrobenzyl	0.5	240-243
15	12(4)	prop-2-ynyl	-CONH-	4-aminobenzyl	0.5	211-215
	13	prop-2-ynyl	-CONH-	4-carboxybenzyl	2	175-179
20	14(5)	prop-2-ynyl	-CONH-	3-carboethoxy- benzyl	1.3	212-216
	15(6)	prop-2-ynyl	-CONH-	3-carboxybenzyl	2.5	164-168
25	16	prop-2-ynyl	-CONH-	3-fluorobenzyl	1	213-218
	17*(7)	prop-2-ynyl	-CONH-	2-nitrobenzyl	2	225-227
30	18*(8)	prop-2-ynyl	-CONH-	3-hydroxybenzyl	2	183-187

NOTES

* The product was purified by chromatography on a silica gel column using increasingly polar mixtures of methylene chloride and ethanol as eluent.

(1) Diethyl cyanophosphonate was used in place of diphenylphosphoryl azide.

(2) Diethyl cyanophosphonate was used in place of diphenylphosphoryl azide. Tert-butyl 4-aminobenzoate is described in Synth. Comm., 1984, 14, 921.

(3) A mixture of Compound No. 2, described immediately above Compound No. 3 in Table II, and trifluoroacetic acid was stirred at laboratory temperature for 10 minutes and evaporated to give the benzoic acid, as its trifluoroacetic acid salt.

(4) 4-Aminobenzylamine is described in J. Med. Chem., 1977, 20, 1189.

(5) 3-Carboethoxybenzyl bromide (1 ml; Heterocycles, 1977, 6, 5) was added to a saturated solution of ammonia in acetonitrile (30 ml) which had been cooled to -30 °C. The mixture was stirred and allowed to warm to laboratory temperature. The mixture was filtered and the filtrate was evaporated. The residue was purified by chromatography on a silica gel column using a 10:1 v/v mixture of ethyl acetate and methanol as eluent. There was thus obtained as an oil 3-carboethoxybenzylamine (0.4 g) which was used without further purification as the appropriate amine in the process described in Example 1.

(6) A portion of Compound No. 14 (obtained as described in note (5) above) was dissolved in methanol and hydrolysed at laboratory temperature by the addition of a 2N aqueous sodium hydroxide solution.

(7) A solution of 2-nitrobenzyl chloride (1.0 g) in acetonitrile (10 ml) was added to a cold (-30 °C) solution of liquid ammonia (10 ml) in acetonitrile (20 ml). The mixture was stirred at -30 to -40 °C for 3 hours and

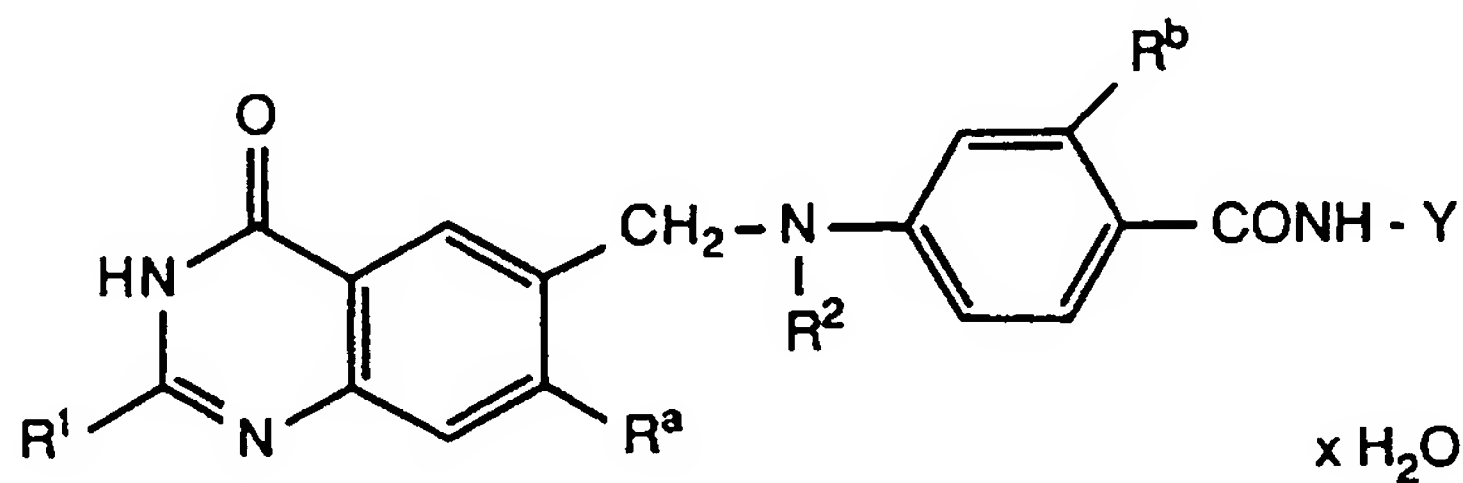
allowed to warm to 20°C. Evaporation left an orange gum which was chromatographed on silica gel using increasingly polar methanol/ethyl acetate mixtures as eluent to give a yellow gum which slowly crystallised. There was thus obtained 2-nitrobenzylamine (0.13 g).

(8) A solution of boron tribromide in methylene chloride (3.6 ml of 1M solution) was added dropwise to a solution of 3-methoxybenzylamine (0.5 g) in methylene chloride (10 ml) which had been cooled to -5°C. The mixture was stirred for 1 hour and then a further 3.6 ml of the boron tribromide solution was added. Stirring was continued at -5°C for 3 hours. The solution was allowed to warm to 20°C, diluted with methylene chloride (30 ml), and the white solid was filtered off. The solid was treated with dilute aqueous sodium bicarbonate solution until the washings were almost neutral. The residual solid was dried. The white solid was slurried with dry dimethylformamide, filtered and the filtrate was evaporated to leave a cream coloured oil. There was thus obtained 3-hydroxybenzylamine (0.17 g).

EXAMPLE 3

The process described in Example 1 was repeated using the appropriate benzoic acid in place of p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, and the appropriate amine in place of 3-aminomethylpyridine. There were thus obtained the compounds described in the following table, the structures of which were confirmed by proton magnetic resonance and mass spectroscopy and by elemental analysis.

TABLE III



Ex. 3	R¹	Rᵃ	R²	Rᵇ	Y	x	m.p.
Compd. No.							(°C)
(Note)							
1(1)*	Me	Me	prop-2-ynyl	H	3-nitrobenzyl	-	251-254
2(2)*	Me	H	Me	F	3-nitrobenzyl	-	269-272
3(3)*	MeO	H	prop-2-ynyl	H	3-nitrobenzyl	0.3	181-185
4(4)	H₂N	H	prop-2-ynyl	H	3-nitrobenzyl	1.3	187-192
5(5)	FCH₂	H	prop-2-ynyl	H	3-nitrobenzyl	0.5	232-234

NOTES

* In these cases the product was purified by column chromatography using increasingly polar mixtures of methylene chloride and ethanol as eluent.

5 (1) p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (as its trifluoroacetic acid salt) was obtained as described in UK Patent Specification No. 2202847A.

(2) p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-o-fluorobenzoic acid (as its trifluoroacetic acid salt) was obtained by repetition of the process described in UK Patent Specification No. 21888319A, in the portion of Example 11 thereof which is concerned with the preparation of starting materials, except that tert-butyl p-amino-o-fluorobenzoate was used in place of tert-butyl p-aminobenzoate, and methyl iodide was used in place of propargyl bromide. There was thus obtained the required starting material in 42% yield, as a white salt with trifluoroacetic acid.

The tert-butyl p-amino-o-fluorobenzoate, used as a starting material, was prepared from o-fluoro-p-nitrobenzoic acid (described in UK Patent Specification No 2175903) by the conventional reactions of esterification with isobutene and by reduction of the tert-butyl ester so formed with iron powder in the presence of acetic acid using the conditions described in UK Patent Specification No. 2175903.

(3) p-[N-(3,4-Dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)aminobenzoic acid, used as a starting material, was obtained as follows:-

N-[p-[N-(3,4-Dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl]-L-glutamic acid (prepared as described in UK Patent Specification No. 2188319A, 0.5g) was dissolved in a tris-(hydroxymethyl)aminomethane buffer solution (80 ml) containing 1N aqueous sodium hydroxide solution (1 ml). The basicity of the solution was adjusted to pH 7.3 and the mixture was warmed to 37°C. Carboxypeptidase G₂ enzyme solution (200 units) was added and the mixture was stirred vigorously at 37°C for 1 hour. The mixture was cooled in ice, acidified to pH 4 by the addition of 1N aqueous hydrochloric acid solution and the white solid was filtered off, washed with water and dried. There was thus obtained the required starting material (0.3 g).

(4) p-[N-(2-Amino-3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid was obtained by the method described in Note (3) above except that N-[p-[N-(2-amino-3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl]-L-glutamate (prepared as described in UK Patent Specification No. 2065653B) was used as the substrate.

(5) The reaction was worked up by pouring the mixture into water and extracting with ethyl acetate (3 x 30 ml). The combined organic extracts were dried (MgSO₄) and evaporated and the residue was purified by column chromatography on silica gel using increasingly polar mixtures of chloroform and methanol as eluent. The resultant solid was triturated with acetone and the solid so obtained was washed with diethyl ether to give the desired product. p-[N-(3,4-Dihydro-2-fluoromethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (as its trifluoroacetic acid salt), used as a starting material, was prepared as follows:-

Using the procedure described in UK Patent Specification No. 2188319A (Example 5 thereof), 6-bromomethyl-2-fluoromethyl-3,4-dihydroquinazolin-4-one was reacted with tert-butyl p-(prop-2-ynylamino)benzoate [prepared by the alkylation of tert-butyl p-aminobenzoate with prop-2-ynyl bromide using the conditions described for related alkylations in *J. Med. Chem.*, 1985, 28, 1468] and the resultant product was treated with trifluoroacetic acid. There was thus obtained the required starting material in 53% yield,

NMR Spectrum (CD₃SOCD₃) 3.32 (1H), 4.38 (2H), 4.84 (2H), 5.18 (1H), 5.42 (1H), 6.85 (2H), 7.6-7.82 (4H), 8.03 (1H).

EXAMPLE 4

Using the process described in Example 1, 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carboxylic acid was reacted with 3-nitrobenzylamine. The product was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethanol as eluent. There was thus obtained 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide (containing 0.7 equivalents of water) in 5% yield, m.p. 245-250°C.

The 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carboxylic acid was obtained as follows:-

Using the method described in *J. Med. Chem.*, 1980, 23, 1405, methyl 5-(N-tert-butoxycarbonylamino)-pyridine-2-carboxylate was reacted with prop-2-ynyl bromide to give methyl 5-[N-tert-butoxycarbonyl]-N-

(prop-2-ynyl)amino]pyridine-2-carboxylate in 90% yield. A mixture of the product so obtained and trifluoroacetic acid was stirred at 0 °C for 1 hour and evaporated. There was thus obtained methyl 5-(N-prop-2-ynylamino)pyridine-2-carboxylate in 90% yield, as a gum.

Using the process described in UK Patent Specification No. 2188319A (Example 6 thereof), the product so obtained was reacted with 2-bromomethyl-3,4-dihydro-2-methylquinazolin-4-one to give the methyl ester of the required starting material and the methyl ester was hydrolysed by conventional treatment with aqueous N sodium hydroxide solution to give the required starting material in 3% overall yield as a gum which was used without further purification.

10 **EXAMPLE 5**

p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl azide (0.53 g) and 3-nitrobenzyl alcohol (0.33 g) were suspended in dry dimethylformamide (20 ml) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.63 ml) was added. The mixture was stirred at laboratory temperature for 18 hours. The volume of the mixture was reduced to about 10 ml by evaporation and the residue was poured into water (50 ml). The precipitated solid was filtered off, washed with water (3 x 10 ml) and dried. The material was triturated with a 4:1 v/v mixture of methylene chloride and ethanol and the resultant solid was dried in air. There was thus obtained 3-nitrobenzyl p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate (containing 0.7 equivalents of water, 0.22 g), m.p. 238-241 °C.

20 **NMR Spectrum** (CD₃SOCD₃) 2.32 (s, 3H, 2-CH₃), 3.22 (s, 1H, C≡CH), 4.36 (s, 2H, CH₂), 4.81 (s, 2H, CH₂), 5.42 (s, 2H, OCH₂), 6.88 (d, 2H, J=8 Hz, aromatic), 7.54 (d, 1H, J=6 Hz, aromatic), 7.63-7.75 (m, 3H, aromatic), 7.84 (d, 2H, J=8 Hz, aromatic), 7.85-7.97 (m, 2H, aromatic), 8.18 (d, 1H, J=6 Hz, aromatic), 8.29 (broad s, 1H, aromatic);

Mass Spectrum: (positive ion FAB) m/e (P + 1) 483;

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Elemental Analysis: Found	C, 65.3;	H, 4.8;	N, 11.5;
C ₂₇ H ₂₂ N ₄ O ₅ ·0.7H ₂ O requires	C, 65.4;	H, 4.7;	N, 11.3%.

30 The p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl azide, used as a starting material, was obtained as follows:

Diphenylphosphoryl azide (2.80 ml) and triethylamine (3.59 ml) were added successively to a mixture of p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-methyl)-N-(prop-2-ynyl)amino]benzoic acid (as its trifluoroacetic acid salt; 3.0 g; UK Patent Specification No. 2188319A) and dimethylformamide (35 ml) which had been cooled to approximately 5 °C by immersion in an ice bath. The mixture was stirred at 5 °C for 3 hours and allowed to stand at 5 °C overnight. The precipitated solid was filtered off, washed in turn with dimethylformamide and diethyl ether and dried. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl azide (2.10 g).

40 **NMR Spectrum:** (CD₃SOCD₃) 2.33 (s, 3H, CH₃), 3.24 (t, 1H, J=1Hz, C≡CH), 4.40 (broad s, 2H, CH₂), 4.85 (s, 2H, CH₂), 6.89 (d, 2H, J=8 Hz, aromatic), 7.54 (d, 1H, J=6 Hz, aromatic), 7.67 (d of d's, 1H, J=6 and 2 Hz, aromatic), 7.78 (d, 2H, J=8 Hz, aromatic), 7.95 (d, 1H, J=2 Hz, aromatic), 12.2 (broad s, 1H, NH);

Mass Spectrum: m/e (P) 372.

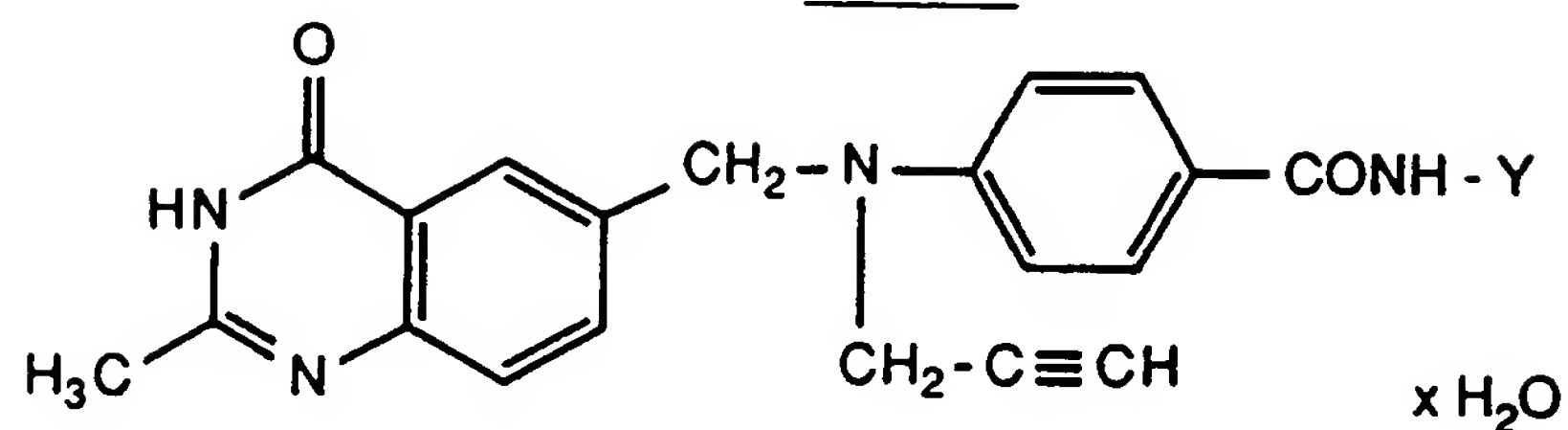
EXAMPLE 6

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The process described in Example 5 was repeated using p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl azide and the appropriate amine in place of 3-nitrobenzyl alcohol. Any modifications to the general experimental procedure are disclosed in the appropriate footnote. There were thus obtained the compounds described in the following table, the structures of which were confirmed by proton magnetic resonance and mass spectroscopy and by elemental analysis.

55

TABLE IV



	Ex. 6.	Y	x	m.p. (°C)
	Compd. No.			
15	(Note)			
	1(1)	2-thienylmethyl	1.3	224-228
20	2	3-thienylmethyl	0.8	238-245
	3	2-furylmethyl	1	196-210
25	4	3-furylmethyl	-	226-227
	5	2-thiazolylmethyl	0.6	238-240
30	6	4-thiazolylmethyl	0.6	206-208
	7	5-thiazolylmethyl	0.8	242-248
40	8	(4-methylthiazol-2-yl)methyl	0.8	246-252
	9	(3,5-dimethylisoxazol-4-yl)methyl	0.3	281-282
45	10(2)	1,2,4-triazol-3-ylmethyl	1.5	116-120

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TABLE IV Cont'd

5

10	Ex. 6. Compd. No. (Note)	Y	x	m.p. (°C)
15	11(2)	(5-methyl-1,2,4-triazol-3-yl)- methyl	1	204-207
20	12(3)	(5-pyrid-4-yl-1,2,4-triazol- 3-yl)methyl	-	210-214
25	13	3-quinolylmethyl	-	250-270 (decomposes)
30	14	4-quinolylmethyl	0.3	190-192
35	15	8-quinolylmethyl	0.3	144-146
40	16	2-[N-(5-nitropyrid-2-yl)amino]- ethyl	1.5	270-272
45	17(4)	1-(tetrazol-5-yl)ethyl	2.3	-
50	18	2-methyl-1-(tetrazol-5-yl)propyl	1	197-200
	19(5)	(4-hydroxy-6-methylpyrimidin-2- yl)methyl	-	261-264
	20(6)	(2,6-dioxypyrimidin-4-yl)methyl	-	305

NOTES

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(1) The concentrated reaction mixture was poured into water. The mixture was acidified to pH6 by the addition of 1N aqueous hydrochloric acid solution. The resultant precipitate was dried and purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethanol

as eluent.

(2) The product also contains two equivalents of trifluoroacetic acid.

(3) The product contains 1.8 equivalents of chloroform.

(4) The product gave the following characteristic NMR signals (CD_3SOCD_3) 1.6 (d, 3H), 2.31 (s, 3H), 3.18 (t, 1H), 4.34 (d, 2H), 4.77 (s, 2H), 5.43 (m, 1H), 6.86 (m, 2H), 7.5-8.0 (m, 5H), 8.67 (m, 1H).

(5) The product contained 0.25 equivalents of trifluoroacetic acid.

(6) Dimethylsulphoxide was used in place of dimethylformamide as the reaction solvent. The product was isolated as its trifluoroacetic acid salt.

Information concerning the amines required for the compounds described in Table IV is given below.

(i) 3-Aminomethylthiophene is described in J. Med. Chem., 1977, 20, 1287.

(ii) The preparation of 3-aminomethylfuran is described below:-

Diethyl azodicarboxylate (5.2 ml) was added dropwise to a stirred suspension of 3-hydroxymethylfuran (3.18 g), phthalimide (4.76 g) and triphenylphosphine (8.5 g) in tetrahydrofuran (25 ml) which was cooled in an ice-bath to keep the temperature of the reaction mixture below 30 °C. The mixture was stirred at laboratory temperature for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica gel using methylene chloride as eluent. There was thus obtained 3-phthalimidomethylfuran (4.48 g).

A mixture of a portion (2 g) of the product so formed, hydrazine hydrate (0.51 ml) and ethanol (30 ml) was heated to 75 °C for 1.5 hours. Concentrated hydrochloric acid (1.67 ml) was added and the mixture was heated to 60 °C for 1 hour. The mixture was cooled in an ice-bath and filtered. The filtrate was evaporated. The residue was triturated in diethyl ether and the precipitated solid was filtered off, washed with diethyl ether and dried. There was thus obtained 3-aminomethylfuran hydrochloride (1.15 g).

(iii) 2-Aminomethylthiazole is described in J. Amer. Chem. Soc., 1950, 72, 4526.

(iv) 4-Aminomethylthiazole is described in J. Amer. Chem. Soc., 1950, 72, 4526.

(v) The preparation of 5-aminomethylthiazole is described below:-

Thionyl chloride (5 ml) was added dropwise to a solution of 5-hydroxymethylthiazole (2.9 g; US Patent No. 4221802) in chloroform (35 ml). The mixture was evaporated to leave, as a dark oil, 5-chloromethylthiazole hydrochloride (4.42 g).

A mixture of the product so obtained, potassium phthalimide (20.8 g) and dimethylacetamide (40 ml) was stirred at laboratory temperature for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and water. The organic phase was dried (MgSO_4) and evaporated. The residue was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 5-phthalimidomethylthiazole (2.18 g).

Using the procedure described in Note (ii) above, the product so obtained was reacted with hydrazine hydrate. There was thus obtained 5-aminomethylthiazole hydrochloride (1.13 g).

NMR Spectrum: (CD_3SOCD_3) 4.35 (q, 2H), 8.03 (s, 1H), 9.12 (s, 1H).

(vi) 2-Aminomethyl-4-methylthiazole is described in Bull. Chem. Soc. Jap., 1973, 46, 3600 [Chem. Abs., 80, 71072n].

(vii) 4-Aminomethyl-3,5-dimethylisoxazole was prepared from 4-chloromethyl-3,5-dimethylisoxazole using the procedure described in the last two paragraphs of Note (v) above.

(viii) 3-Aminomethyl-1,2,4-triazole is described in Chem. Ber., 1964, 97, 528.

(ix) 3-Aminomethyl-5-methyl-1,2,4-triazole is described in Chem. Ber., 1964, 97, 528.

(x) Using an analogous procedure to that described in Chem. Ber., 1964, 97, 528, except that N-formyl-N'-(4-pyridyl)hydrazine was used in place of N-formylhydrazine, there was thus obtained 3-aminomethyl-5-(4-pyridyl)-1,2,4-triazole which showed the following NMR signals (CDCl_3) 3.89(s, 2H), 7.89(m, 2H), 8.64(m, 2H).

(xi) 3-Aminomethylquinoline is described in Chem. Pharm. Bull., 1966, 14, 566.

(xii) 4-Aminomethylquinoline is described in Chem. Abs., 95, 97545d.

(xiii) The preparation of 8-aminomethylquinoline is described below:-

A mixture of 8-methylquinoline (0.95 ml), N-bromosuccinimide (1.86 g), benzoyl peroxide (0.1 g) and carbon tetrachloride (15 ml) was heated to reflux for 2.5 hours and irradiated with the light from a 250 watt lamp. The mixture was cooled, filtered and evaporated. There was thus obtained 8-bromomethylquinoline (2.18 g).

A mixture of a portion (1.4 g) of the product so obtained, sodium azide (2.43 g) and dimethylformamide (20 ml) was stirred at laboratory temperature for 2.5 hours. A second portion of sodium azide (1.62 g) was added and the mixture was heated to 100 °C for 2 hours. The mixture was evaporated and

the residue was partitioned between methylene chloride and water. The organic phase was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel using a 1:1 v/v mixture of methylene chloride and hexane as eluent. There was thus obtained 8-azidomethylquinoline (1 g).

A mixture of the product so obtained, 10% palladium-on-charcoal catalyst (0.2 g), methanol (5 ml) and ethyl acetate (20 ml) was stirred under an atmosphere of hydrogen for 3 hours. The mixture was filtered and the filtrate was evaporated. There was thus obtained 8-aminomethylquinoline (0.73 g).

(xiv) 5-(1-Amino-2-methylpropyl)tetrazole is described in Tetrahedron, 1971, 27, 1783.

(xv) 2-Aminomethyl-4-hydroxy-6-methylpyrimidine was obtained as follows:-

A mixture of 2-phthalimidoacetimidate hydrochloride (6 g, Chem. Ber., 1964, 97, 528) and a saturated aqueous potassium carbonate solution (50 ml) was stirred at ambient temperature for 3 minutes and then extracted with chloroform. The organic phase was dried (Na_2SO_4) and evaporated. A mixture of the solid so obtained, ammonium chloride (1.4 g) and methanol (100 ml) was stirred at laboratory temperature for 18 hours. The mixture was evaporated to give 2-phthalimidoacetamidine hydrochloride, as a white solid (5.5 g).

A solution of ethyl acetoacetate (2.72 g) in methanol (50 ml) was added to sodium hydride (55% w/w dispersion in mineral oil, 0.73 g). A portion (2 g) of the acetamidine hydrochloride was added and the mixture was heated to reflux for 18 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and dilute aqueous acetic acid solution. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel using a 49:1 v/v mixture of chloroform and methanol as eluent. There was thus obtained 4-hydroxy-6-methyl-2-phthalimidomethylpyrimidine (0.77 g), as a white solid.

NMR Spectrum: (CD_3SOCD_3) 2.06 (s, 3H), 4.67 (s, 2H), 6.06 (s, 1H), 7.9 (m, 4H).

Hydrazine hydrate (0.09 ml) was added to a suspension of the product so obtained (0.48 g) in methanol (20 ml) and the mixture was heated to reflux for 3 hours. The mixture was filtered and the filtrate was evaporated. A mixture of the solid so obtained and 2N aqueous hydrochloric acid solution was heated to 40 °C for 20 minutes. The mixture was filtered and the filtrate was evaporated. There was thus obtained the required starting material, as an orange solid (0.32 g).

(xv) 4-Aminomethyl-2,6-dioxypyrimidine is described in Acta Pol. Pharm., 1970, 27, 341.

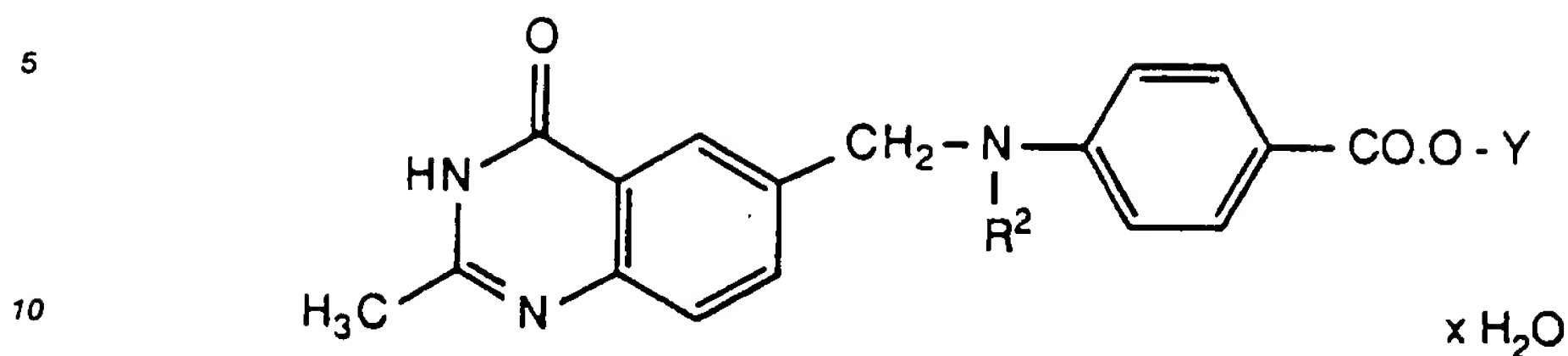
EXAMPLE 7

Using the process described in Example 5, p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]benzoyl azide was reacted with (1-benzylimidazol-2-yl)methylamine to give N-(1-benzylimidazol-2-yl)methyl-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]benzamide (containing 1.3 equivalents of water) in 21% yield, m.p. 217-221 °C.

EXAMPLE 8

The process described in Example 5 was repeated using the appropriate benzoyl azide and the appropriate alcohol in place of 3-nitrobenzyl alcohol. There were thus obtained the compounds described in the following table, the structures of which were confirmed by proton magnetic resonance and mass spectroscopy and by elemental analysis.

TABLE V



Ex. 8	R ²	Y	x	m.p.
Compd. No.				(°C)
(Note)				
1	prop-2-ynyl	(1-benzylimidazol-2-yl)-methyl	0.8	205-209
2(1)	Me	[1-(2-nitrobenzyl)-imidazol-2-yl]methyl	2.5	113-115
3(1)	Me	[1-(4-nitrobenzyl)-imidazol-2-yl]methyl	-	gum
4	prop-2-ynyl	(1-benzyl-4-ethoxycarbonyl-imidazol-2-yl)methyl	1	215-217
5	prop-2-ynyl	(1-benzyl-4-carbamoyl-imidazol-2-yl)methyl	-	170-173
6(1)	Me	1,2,4-triazol-1-ylmethyl	0.5	286-290
7	Et	1,2,4-triazol-1-ylmethyl	1	231-235
8	prop-2-ynyl	1,2,4-triazol-1-ylmethyl	0.5	248-250
9(2)	prop-2-ynyl	(1-benzylimidazol-4-yl)methyl	1	salt

NOTES

(1) p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]benzoic acid, used as the starting material for the appropriate benzoyl azide, was prepared as follows:-

A mixture of 6-bromomethyl-2-methylquinazolin-4-one (15 g, prepared as described in UK Patent Specification No. 2188319A), 4-methylaminobenzoic acid (18 g) and dimethylformamide (150 ml) was heated to 60 °C for 16 hours. The mixture was cooled to laboratory temperature and the precipitate was filtered off, washed with dimethylformamide (100 ml) and dried. The solid was dissolved in trifluoroacetic acid (100 ml) and the solution was evaporated. The resultant salt was triturated under ethyl acetate, filtered off and dried. There was thus obtained the required benzoic acid (as its trifluoroacetic acid salt; 17 g).

(2) The product also contained two equivalents of trifluoroacetic acid and showed the following characteristic NMR signals (CD_3SOCD_3) 2.36 (s, 3H), 3.21 (t, 1H), 4.36 (d, 2H), 4.81 (s, 2H), 5.25 (s, 3H), 5.39 (s, 2H), 6.85 (m, 2H), 7.35-7.96 (m, 12H), 9.1 (m, 1H).

Information concerning the preparation of the necessary amine starting materials is provided below:-

(i) The procedure described in *J. Amer. Chem. Soc.*, 1949, 383 was repeated except that 2-nitrobenzyl bromide was used in place of benzyl bromide. There was thus obtained 2-hydroxymethyl-1-(2-nitrobenzyl)imidazole which showed the following NMR signals (CDCl_3) 4.65(s, 2H), 5.69(s, 2H), 6.71-7.62(m, 5H), 8.19(m, 1H).

(ii) The procedure described in *J. Amer. Chem. Soc.*, 1949, 383 was repeated except that 4-nitrobenzyl bromide was used in place of benzyl bromide. There was thus obtained 2-hydroxymethyl-1-(4-nitrobenzyl)imidazole which showed the following NMR signals (CDCl_3) 4.62(s, 2H), 5.37(s, 2H), 6.85(d, 1H), 6.95(d, 1H), 7.3(d, 2H), 8.2(d, 2H).

(iii) Using the procedure described in *J. Amer. Chem. Soc.*, 1949, 383, ethyl imidazole-4-carboxylate was converted into ethyl 1-benzyl-2-hydroxymethylimidazole-4-carboxylate which showed the following NMR signals (CDCl_3) 1.35(t, 2H), 2.95(s, 1H), 4.32(q, 3H), 4.72(s, 2H), 5.26(s, 2H), 7.14-7.4(m, 5H), 7.51(s, 1H).

(iv) A mixture of ethyl 1-benzyl-2-hydroxymethylimidazole-4-carboxylate (described immediately above, 1 g), an aqueous ammonium hydroxide solution (specific gravity 0.88 g/ml, 60 ml) and ethanol (25 ml) was stirred at laboratory temperature for 48 hours and then heated to 50 °C for 4 hours. The mixture was evaporated to give 1-benzyl-2-hydroxymethylimidazole-4-carboxamide, m.p. 204-207 °C.

(v) 1-Hydroxymethyl-1,2,4-triazole is described in European Patent Specification No. 0060222.

(vi) 1-Benzyl-4-hydroxymethylimidazole was prepared as follows:-

Ethyl imidazole-4-carboxylate (15 g) was added to a suspension of sodium hydride (55% w/w dispersion in mineral oil, 4.7 g) in dimethylformamide (50 ml) which had been cooled to 0 °C. The mixture was stirred at 0 °C for 1 hour. A solution of benzyl bromide (15 ml) in dimethylformamide (75 ml) was added and the mixture was stirred at laboratory temperature for 60 minutes. The mixture was poured onto ice (800 ml) and extracted with chloroform. The organic phase was dried (MgSO_4) and evaporated. The residue was purified by column chromatography on silica gel using a 4:1 v/v mixture of chloroform and hexane as eluent. There was thus obtained ethyl 1-benzylimidazole-4-carboxylate (17 g).

Lithium aluminium hydride (1M solution in diethyl ether, 11 ml) was added to a solution of a portion (2.3 g) of the product so obtained in diethyl ether (50 ml) and the mixture was stirred at laboratory temperature for 18 hours. Water (10 ml), aqueous sodium hydroxide solution (10%, 20 ml) and water (10 ml) were added in turn and the mixture was stirred for 15 minutes. The mixture was filtered and the filtrate was extracted with ethyl acetate. The organic layer was dried (MgSO_4) and evaporated. The residue was purified by column chromatography on silica gel using a 97:3 v/v mixture of chloroform and methanol as eluent. There was thus obtained the required starting material (1.2 g)

NMR Spectrum: (CDCl_3) 4.15(s, 1H), 4.55(s, 2H), 5.04(s, 2H), 6.82(d, 1H), 7.1-7.46(m, 6H).

EXAMPLE 9

The process described in Example 5 was repeated using the appropriate benzoyl azide, and the appropriate amine in place of 3-nitrobenzyl alcohol. There were thus obtained the compounds described in the following table, the structures of which were confirmed by proton magnetic resonance and mass spectroscopy and by elemental analysis.

TABLE VI

Chemical structure: A quinazolinone ring with a methyl group at position 2 and a $\text{CH}_2\text{-N(R}^2\text{)-C}_6\text{H}_4\text{-CONH-Y}$ group at position 4.

Ex. 9	R ²	Y	x	m.p. (°C)
1*	prop-2-ynyl	3-methylbenzyl	0.7	196-198
2*	prop-2-ynyl	3-methoxybenzyl	-	214-216
3*	prop-2-ynyl	3-trifluoromethylbenzyl	0.5	237-238
4(1)	prop-2-ynyl	3-cyanobenzyl	0.8	245-246
5*	Me	3-nitrobenzyl	-	250-253

NOTES

* The product was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethanol as eluent.

(1) 3-Cyanobenzylamine is described in *J. Med. Chem.*, 27, 1111.

EXAMPLE 10

Oxalyl chloride (0.114 ml) was added dropwise to a stirred solution of p-[N-(3,4-dihydro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (0.39 g) in a mixture of methylene chloride (15 ml) and one drop of dimethylformamide which had been cooled to approximately 0°C. After an initial vigorous reaction, the pale yellow suspension was stirred at 20°C for 2 hours. The mixture was evaporated, the residue was resuspended in methylene chloride (15 ml) and the mixture was cooled to 5°C. A mixture of triethylamine (0.36 ml) and 4-fluorobenzylamine (0.11 g) in methylene chloride (2 ml) was added and the clear solution was stirred at 20°C for 18 hours. The solution was washed with water (2 x 15 ml), dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica gel using increasingly polar mixtures of ethyl acetate and petrol (b.p. 60-80°C) as eluent. There was thus obtained p-[N-(3,4-dihydro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(4-fluorobenzyl)benzamide, as a pale yellow oil (242 mg).

The product so obtained was dissolved in ethanol (5 ml) and aqueous 2N sodium hydroxide solution was added. The solution was stirred at laboratory temperature for 2 hours. The mixture was evaporated and the residue was taken up in distilled water (10 ml). The mixture was acidified to pH 3 by the addition of 1N aqueous hydrochloric acid solution. The precipitate was filtered off, washed with water (3 x 5 ml), and dried *in vacuo* at 70°C for 4 hours. There were thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(4-fluorobenzyl)benzamide (containing 0.75 equivalents of water, 0.13 g),

m.p. 208-210 °C. NMR Spectrum: (CD₃SOCD₃) 2.35 (s, 3H, CH₃), 3.18 (t, 1H, J = 1.5 Hz, C≡CH), 4.32 (broad s, 2H, CH₂), 4.41 (d, 2H, J = 6 Hz, NHCH₂), 4.77 (s, 2H, CH₂), 6.84 (d, 2H, J = 8 Hz, aromatic), 7.05-7.17 (m, 2H, aromatic), 7.25-7.38 (m, 2H, aromatic), 7.54 (d, 1H, J = 6 Hz, aromatic), 7.68 (d of d's, 1H, J = 6 and 2 Hz, aromatic), 7.75 (d, 1H, J = 8 Hz, aromatic), 7.98 (d, 1H, J = 2 Hz, aromatic), 8.68 (t, 1H, J = 6 Hz, CONHCH₂);
 Mass Spectrum: (positive ion FAB) m/e (P + 1) 455;

Elemental Analysis: Found	C, 68.5;	H, 5.4;	N, 12.3;
C ₂₅ H ₂₃ N ₄ O ₂ F. 0.75 H ₂ O requires	C, 68.6;	H, 5.0;	N, 11.6%

The p[N-(3,4-dihydro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-benzoic acid, used as a starting material, was obtained as follows:-

Sodium hydride (6.62 g of a 50% w/w dispersion in mineral oil) was added portionwise to a cold (0-5 °C; ice-bath), stirred solution of 2,6-dimethylquinazolin-4-one (20.0 g) in dimethylformamide (125 ml). The mixture was stirred at 5 °C for 1 hour. Chloromethyl pivalate (19.8 ml) was added in one portion and the creamy mixture was allowed to warm to laboratory temperature and was stirred for a further 18 hours. The mixture was cooled to 10 °C and aqueous 1N hydrochloric acid solution was added (45 ml). Ethyl acetate (200 ml) was added and the organic layer was separated and combined with further ethyl acetate extracts (2 x 100 ml). The combined organic fractions were washed with water (3 x 200 ml), dried and evaporated. The residue was triturated with cold hexane and the white solid was filtered off, washed with hexane and dried. There was thus obtained 3-(pivaloyloxymethyl)-2,6-dimethylquinazolin-4-one (17.22 g), m.p. 95-98 °C. NMR Spectrum: (CDCl₃) 1.24 (s, 9H, 3 x CH₃), 2.48 (s, 3H, ArCH₃), 2.63 (s, 3H, ArCH₃), 6.13 (s, 2H, OCH₂N), 7.52 (d, 1H, J = 8 Hz, aromatic), 7.57 (d of d's, 1H, J = 8 and 1.5 Hz, aromatic), 8.05 (d, 1H, J = 1.5 Hz, aromatic);
 Mass Spectrum: m/e (P) 288.

The product so obtained (15.02 g) was dissolved in warm carbon tetrachloride (280 ml) and powdered N-bromosuccinimide (9.8 g) and benzoyl peroxide (0.2 g) were added successively. The mixture was stirred vigorously and heated to reflux for 3.5 hours. The hot solution was filtered and the filtrate was evaporated to leave a residue which was triturated with cold hexane. The white solid was filtered off and dried. There was thus obtained 6-bromomethyl-2-methyl-3-pivaloyloxymethylquinazolin-4-one (11.72 g), NMR Spectrum: (CDCl₃) 1.22 (s, 9H, 3x CH₃), 2.65 (s, 3H, ArCH₃), 4.58 (s, 2H, CH₂Br), 6.12 (s, 2H, OCH₂N), 7.53 (d, 1H, J = 8.5 Hz, aromatic), 7.79 (d of d's, 1H, J = 8.5 and 2 Hz, aromatic), 8.27 (d, 1H, J = 2 Hz, aromatic);
 Mass Spectrum: (positive ion FAB) m/e (P + 1) 367.

After repetition of the above reaction steps, 2,6-lutidine (10 ml) was added to a mixture of the product so obtained (39.6 g), tert-butyl p[N-(prop-2-ynyl)amino]benzoate (20.0 g) and dimethylformamide (280 ml). The solution was heated to 70-75 °C for 18 hours. The brown solution was cooled to laboratory temperature and poured onto a mixture of ice and water (1 L). The mixture was filtered and the residue was washed with cold water (2 x 100 ml) and dried. The solid was triturated in cold diethyl ether (300 ml). The white solid was filtered off, washed with ether (2 x 50 ml) and dried. There was thus obtained tert-butyl p-[N-(3,4-dihydro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate (28.6 g). NMR Spectrum: (CDCl₃) 1.23 (s, 9H, 3 x CH₃), 1.55 (s, 9H, 3 x CH₃), 2.27 (t, 1H, J = 1.5 Hz, C≡CH), 2.63 (s, 3H, ArCH₃), 4.17 (broad s, 2H, CH₂), 4.73 (s, 2H, CH₂), 6.11 (s, 2H, OCH₂N), 6.81 (d, 2H, J = 8 Hz, aromatic), 7.59 (d, 1H, J = 8 Hz, aromatic), 7.67 (d of d's, 1H, J = 8 and 1.5 Hz, aromatic), 7.87 (d, 2H, J = 8 Hz, aromatic), 8.18 (d, 1H, J = 1.5 Hz, aromatic);
 Mass Spectrum: m/e (P) 517.

The product so obtained (28 g) was added in portions to stirred trifluoroacetic acid (100 ml) and the solution was stirred at laboratory temperature under an argon atmosphere for 3 hours. Evaporation left a residue which was triturated under diethyl ether (350 ml). The precipitate was filtered off, washed with cold ether (2 x 50 ml) and dried to give an off-white solid. There was thus obtained p-[N-(3,4-dihydro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (containing 0.7 equivalents of trifluoroacetic acid, 21.0 g), m.p. 143 °C.

NMR Spectrum: (CDCl₃) 1.23 (s, 9H, 3 x CH₃), 2.32 (t, 1H, J = 1 Hz, C≡CH), 2.65 (s, 3H, ArCH₃), 4.19 (broad s, 2H, CH₂), 4.79 (s, 2H, CH₂), 6.12 (s, 2H, OCH₂N), 6.85 (d, 2H, J = 8 Hz, aromatic), 7.64 (d, 1H, J = 8 Hz, aromatic), 7.69 (d of d's, 1H, J = 8 and 1.5 Hz, aromatic), 7.98 (d, 2H, J = 8 Hz, aromatic), 8.18 (d, 1H, J = 1.5 Hz, aromatic);

Mass Spectrum: (positive ion FAB) m/e (P + 1) 462;

Elemental Analysis: Found	C, 65.0;	H, 5.9;	N, 8.6;
$C_{26}H_{27}N_3O_5 \cdot 0.7CF_3COOH$ requires	C, 65.0;	H, 5.5;	N, 8.3%.

5

EXAMPLE 11

The process described in Example 10 was repeated using the appropriate amine or sulphonamide in place of 4-fluorobenzylamine. There were thus obtained the compounds described in the following table, the structures of which were confirmed by proton magnetic resonance and mass spectrometry and by
10 elemental analysis.

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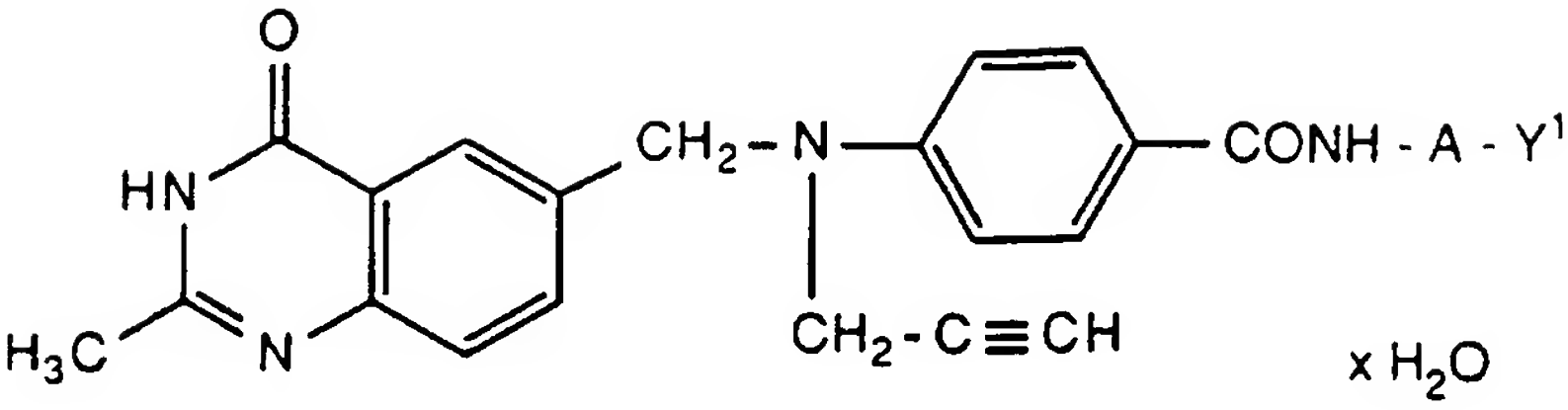
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TABLE VII



15

Ex. 11	A-Y ¹	x	m.p.
Compd. No.			(°C)
(Note)			
1	2-fluorophenyl	1.5	235-237
2	3-fluorophenyl	0.5	269-271
3	4-fluorophenyl	1.5	249-252
4	4-carboxymethylphenyl	1.8	270-274
5	4-(1-carboxyethyl)phenyl	1.5	185-187
6	4-(carboxypropyl)phenyl	3	290-295
7*	2,4-difluorobenzyl	1.5	211-213
8*	2,6-difluorobenzyl	1.3	198-200
9*	4-sulphamoylphenyl	-	275-278
10	2-(4-nitrophenyl)ethyl	3.8	255-256
11	3-isoxazolylmethyl	-	255-256
12 ⁺	4-nitrophenylsulphonyl	3	155-160

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TABLE VII Cont'd

Ex. 11	A-Y ¹	x	m.p.
Compd. No.			(°C)
(Note)			
13 ⁺	4-methoxyphenylsulphonyl	1	260
14 ⁺	4-fluorophenylsulphonyl	1.8	272-277
15	3-nitrophenyl	1.5	195-205
16	(2-chloropyrid-4-yl)methyl	-	245-246
17	(6-hydroxypyrid-2-yl)methyl	-	267-272
18(1)	(2-benzimidazolyl)methyl	1	salt

NOTES

* Elemental analysis showed that the product also contained 1 equivalent of sodium hydroxide.

+ In these cases the appropriate arylsulphonamide was used in place of an amine. The pivaloyloxymethyl protecting group was removed using the following procedure:-

The appropriate acylsulphonamide so obtained was dissolved in methanol (50 ml) which had been saturated with gaseous ammonia. The mixture was stirred at laboratory temperature for 18 hours. The mixture was evaporated and the residue was purified by column chromatography on a reversed-phase preparative h.p.l.c. column (Dymamax 60 A) using decreasingly polar mixtures of methanol and water as eluent.

(1) The product was obtained as the hydrochloride salt and showed the following characteristic NMR signals (CD₃SOCD₃) 2.36 (s, 3H), 3.2 (t, 1H), 4.38 (d, 2H), 4.82 (s, 2H), 6.89 (m, 2H), 7.36-8.0 (m, 9H), 9.09 (m, 1H).

Information concerning the preparation of the amine starting materials is provided below:-

(i) The preparation of 3-aminomethylisoxazole is described below:-

Di-isobutylaluminium hydride (1.5 M in toluene, 29 ml) was added to a solution of ethyl isoxazole-3-carboxylate (6.1 g; *Can. J. Chem.*, 1970, **48**, 475) in toluene (20 ml) which was cooled in an ice-bath. The mixture was stirred at laboratory temperature for 16 hours. The analysis indicated that the reduction was incomplete. A second portion of di-isobutylaluminium hydride (28.8 ml) was added and the mixture was stirred for 16 hours. The bulk of the toluene was evaporated and the mixture was poured into a saturated aqueous ammonium chloride solution. The precipitate was filtered off and dried. There was thus obtained 3-hydroxymethylisoxazole (2.1 g).

Thionyl chloride (4.2 ml) was added dropwise to a solution of the product so obtained in chloroform (20 ml) and the mixture was stirred at laboratory temperature for 1 hour. The mixture was evaporated and the crude 3-chloromethylisoxazole so obtained was used without further purification. The crude product was dissolved in dimethylacetamide (10 ml). Sodium carbonate (approx. 3 g) was added portionwise until the acidity of the reaction mixture was neutralised. Sodium azide (1 equivalent) was

added and the mixture was stirred at laboratory temperature for 1.8 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel using a 1:1 v/v mixture of methylene chloride and hexane as eluent. There was thus obtained 3-azidomethylisoxazole (1.15 g). NMR Spectrum: (CD_3SOCD_3) 4.6 (s, 2H), 6.65 (d, 1H), 8.95 (d, 1H).

A mixture of the product so obtained, 10% palladium-on-charcoal catalyst (0.22 g) and ethyl acetate (10 ml) was stirred under an atmosphere of hydrogen for 2.5 hours. The mixture was filtered and the filtrate was evaporated. There was thus obtained 3-aminomethylisoxazole (0.93 g).

(ii) The preparation of methyl 4-(4-aminophenyl)butyrate is described below:-

Thionyl chloride (6.9 ml) was added to 4-(4-nitrophenyl)butyric acid (10.0 g) which was heated to reflux for 2 hours. The clear solution was cooled and the excess of thionyl chloride was evaporated. The residue was dissolved in methylene chloride (25 ml) and added dropwise to a stirred mixture of methanol (7.6 ml) and pyridine (4.59 ml) in methylene chloride (100 ml) which had been cooled to -5°C by immersion in an ice-bath. The mixture was stirred at 20°C for 18 hours, washed with dilute aqueous sodium bicarbonate solution, and with water and dried. There was thus obtained methyl 4-(4-nitrophenyl)-butyrate (9.68 g).

The material so obtained was dissolved in a mixture of methanol (200 ml) and water (100 ml) and heated to reflux on a steam bath. Ferrous sulphate heptahydrate (11.71 g) and iron powder (34.0 g) were added and the mixture was heated to reflux for 6 hours. The solution was filtered whilst hot. Methanol was evaporated from the filtrate and the residual aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried and evaporated to give a residue which was purified by column chromatography on silica gel using methylene chloride as eluent. There was thus obtained methyl 4-(4-aminophenyl)butyrate (6.22 g).

(iii) Methyl 2-(4-aminophenyl)propanoate was obtained from 2-(4-nitrophenyl)propionic acid by a procedure analogous to that described immediately above.

(iv) The preparation of 4-fluorobenzenesulphonamide is described below:-

A solution of 4-fluorobenzenesulphonyl chloride (2.0 g) in dry tetrahydrofuran (5 ml) was added dropwise to a cold (ice-bath), stirred solution of aqueous ammonia (S.G. 0.88, 20 ml). After the addition, stirring was continued for 30 minutes and the precipitated solid was filtered off, washed with water and dried in air. There was thus obtained 4-fluorobenzenesulphonamide (0.70 g).

(v) p-Methoxybenzenesulphonamide was obtained from 4-methoxybenzenesulphonyl chloride using the procedure described immediately above.

(vi) The preparation of 4-aminomethyl-2-chloropyridine is described below:-

A mixture of 2-chloro-4-cyanopyridine (1.9 g), platinum dioxide (0.3 g), acetic anhydride (50 ml) and acetic acid (50 ml) was stirred under an atmosphere of hydrogen for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between chloroform and dilute aqueous sodium bicarbonate solution. The organic phase was dried (MgSO_4) and evaporated to give N-(2-chloropyrid-4-ylmethyl)acetamide (1.5 g), as an oil.

A mixture of the product so obtained and 6N aqueous hydrochloric acid (72 ml) was heated to reflux for 21 hours. The mixture was evaporated and the residue was triturated in a 2:1 v/v mixture of methylene chloride and methanol. There was thus obtained the required starting material (0.53 g), as its hydrochloride salt. NMR Spectrum (CD_3SOCD_3) 4.10 (s, 2H), 7.55 (d, 1H), 7.69 (s, 1H), 8.46 (d, 1H), 8.68 (broad s, 2H).

(vii) The 2-aminomethyl-6-hydroxypyridine, used as a starting material, is described in US Patent No. 4496734.

EXAMPLE 12

Water (0.5 ml) and triethylamine (0.34 ml) were added to a mixture of p-[N-3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl azide (0.15 g) and 3-aminosuccinimide (J. Amer. Chem. Soc., 1954 76, 2467; 0.14 g) in dimethylsulfoxide (5 ml). The mixture was stirred at laboratory temperature for 10 days and evaporated. The residue was triturated with water, dried, triturated with diethyl ether and dried again. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2,5-dioxopyrrolidin-3-yl)benzamide (containing 1 equivalent of water, 0.13 g), m.p. 164-185°C (decomposes).

NMR Spectrum: (CD_3SOCD_3) 2.32 (s, 3H, CH_3), 2.5-2.7 (m, 1H), 2.8-3.0 (m, 1H), 3.17 (s, 1H, $\text{C}\equiv\text{CH}$), 4.32 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 6.85 (d, 2H, $J=8$ Hz, aromatic), 7.54 (d, 1H, $J=6$ Hz, aromatic), 7.62-7.74 (m, 3H, aromatic), 7.96 (broad s, 1H, aromatic), 8.73 (d, 1H, $J=6$ Hz, CONH), 11.18 (s, 1H, CONHCO);

Mass Spectrum: (positive ion FAB) m/e (P + 1) 443;

Elemental analysis: Found	C, 62.7;	H, 4.5;	N, 14.8;
C ₂₄ H ₂₁ N ₅ O ₄ · H ₂ O requires	C, 62.4;	H, 5.0;	N, 15.2%.

EXAMPLE 13

A mixture of 6-bromomethyl-2-methylquinazolin-4-one (0.45 g), 2,6-lutidine (0.30 ml), N²-(3-fluorophenyl)-4-ethylaminobenzohydrazide (0.48 g) and dimethylacetamide (10 ml) was heated to 80 °C for 4 hours. The mixture was cooled to laboratory temperature, poured into water (50 ml) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with water (2 x 25 ml), dried and evaporated to leave a residue which was purified by column chromatography on silica gel using increasingly polar mixtures of ethyl acetate and petrol (b.p. 60-80 °C) as eluent. There was thus obtained N²-(3-fluorophenyl)-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]benzohydrazide (containing 1.5 equivalents of water, 0.11 g).

NMR Spectrum (CD₃SOCD₃): 1.15 (t, 2H, J = 7 Hz, CH₂CH₃), 2.34 (s, 3H, CH₃), 3.35-3.70 (m, 3H, C≡CH and CH₂CH₃), 4.75 (broad s, 2H, CH₂), 6.40-6.80 (m, 5H, aromatic and NH), 7.10-7.35 (m, 1H, aromatic), 7.55-8.0 (m, 7H, aromatic and NH);

Mass Spectrum (positive ion FAB): m/e (P + 1) 474;

Elemental Analysis: Found,	C, 63.4;	H, 5.6;	N, 14.0;
C ₂₅ H ₂₄ N ₅ O ₂ F · 1.5H ₂ O requires	C, 63.6;	H, 5.8;	N, 14.8%.

The N²-(3-fluorophenyl)-p-ethylaminobenzohydrazide, used as a starting material, was obtained as follows:-

A solution of 4-nitrobenzoyl chloride (3.58 g) in methylene chloride (50 ml) was added dropwise to a stirred mixture of 3-fluorophenylhydrazinehydrochloride (3.14 g), pyridine (3.12 ml) and methylene chloride (50 ml) which had been cooled to 5 °C. The mixture was stirred at 5 °C for 1 hour and at 20 °C for 2 hours. The yellow precipitate was filtered off, washed with methylene chloride and dried. There was thus obtained N²-(3-fluorophenyl)-p-nitrobenzohydrazide (3.25 g).

A solution of the product so obtained in acetic acid (40 ml) was heated to 80 °C and iron powder (7.26 g) was added portionwise. The mixture was stirred at 80 °C for 2.5 hours, cooled to laboratory temperature and filtered. The filtrate was washed with water (3 x 50 ml), dried (MgSO₄) and evaporated. There was thus obtained N²-(3-fluorophenyl)-p-aminobenzohydrazide (2.29 g).

Using the procedure described in UK Patent Specification No. 2188319A for the N-alkylation of diethyl N-(4-aminobenzoyl)-L-glutamate, the hydrazide so obtained was reacted with ethyl iodide. There was thus obtained the required starting material (1.5 g).

EXAMPLE 14

Diphenylphosphoryl azide (0.09 ml) and triethylamine (0.12 ml) were added in turn to a solution of N-(4-carboxybenzyl)-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamide (prepared as described in Example 2, 0.13 g) in dimethylsulfoxide (10 ml). The mixture was stirred at laboratory temperature for 45 minutes. Aqueous methylamine (33% w/v; 0.05 ml) was added and the mixture was stirred at laboratory temperature for 18 hours. The solution was poured into water (50 ml) and stirred. The precipitate was isolated, washed with water and dried. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-[4-(N-methylcarbamoyl)benzyl]-benzamide (containing 1.3 equivalents of water, 79 mg), m.p. 260-263 °C.

NMR Spectrum: (CD₃SOCD₃) 2.32 (s, 3H, CH₃), 2.77 (d, 3H, J = 4 Hz, NHCH₃), 3.17 (t, 1H, J = 1.5 Hz, C≡CH), 4.31 (broad s, 2H, CH₂), 4.48 (d, 2H, J = 6 Hz, NHCH₂), 4.76 (s, 2H, CH₂), 6.85 (d, 2H, J = 8 Hz, aromatic), 7.34 (d, 2H, J = 7 Hz), 7.53 (d, 1H, J = 7 Hz, aromatic), 7.65-7.80 (m, 5H, aromatic), 7.97 (d, 1H, J = 2 Hz, aromatic) 8.32 (broad hump, 1H, NH), 8.72 (t, 1H, J = 6 Hz, NH);

Mass Spectrum (positive ion FAB): m/e (P + 1) 494;

Elemental analysis: Found	C, 67.8;	H, 5.6;	N, 13.2;
C ₂₉ H ₂₇ N ₅ O ₃ . 1.3H ₂ O requires	C, 67.5;	H, 5.7;	N, 13.6%.

5

EXAMPLE 15

Diphenylphosphoryl azide (0.55 ml) and triethylamine (1.3 ml) were added in turn to a mixture of p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-nitrobenzoic acid (0.457 g), 3-nitrobenzylamine hydrochloride (0.66 g) and dimethylacetamide (4 ml) and the mixture was stirred at laboratory temperature for 16 hours. The mixture was evaporated and the residue was triturated in water to give crude product as a solid. The aqueous mother liquors were extracted with ethyl acetate. The organic extract was dried (MgSO₄) and evaporated to give a second portion of crude product. The portions of product were combined and purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethanol as eluent. The product was further purified by column chromatography on a reversed-phase h.p.l.c. column (Dynamax) eluting with a 3:2 v/v mixture of trifluoroacetic acid and water. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-nitro-N-(3-nitrobenzyl)benzamide (containing 0.3 equivalents of trifluoroacetic acid, 0.165 g), m.p. 258-262 °C (decomposes);

20

Elemental Analysis: Found	C, 58.9;	H, 4.0;	N, 13.9;
C ₂₇ H ₂₂ N ₆ O ₆ . 0.3 CF ₃ CO ₂ H requires	C, 58.9;	H, 4.0;	N, 14.9%.

The p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-nitrobenzoic acid, used as a starting material, was obtained as follows:-

A mixture of methyl 4-amino-2-nitrobenzoate (10.6 g; Chem. Abs., 98, 143133e), 2,6-lutidine (8.14 ml), prop-2-ynyl bromide (80% w/w solution in toluene; 7.82 ml) and dimethylacetamide (50 ml) was heated to 80 °C for 4 hours. A second portion of prop-2-ynyl bromide solution (7.82ml) was added and the mixture was heated to 80 °C for 5 hours. The mixture was cooled to laboratory temperature and partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica gel using methylene chloride as eluent. There was thus obtained methyl 2-nitro-4-(prop-2-ynylamino)benzoate (6.58 g), m.p. 134-135 °C.

A mixture of a portion (2 g) of the ester so obtained, 6-bromomethyl-3,4-dihydro-2-methylquinazolin-4-one (2.6 g), 2,6-lutidine (2 ml) and dimethylacetamide (10 ml) was heated to 80 °C for 4 hours. The mixture was cooled to laboratory temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, dried (MgSO₄) and evaporated. The residue was triturated in ethyl acetate to give methyl p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-nitrobenzoate (1.52 g).

A mixture of the product so obtained, 1N aqueous sodium hydroxide solution (18.5 ml) and ethanol (18.5 ml) was stirred at laboratory temperature for 2 hours. The mixture was concentrated by evaporation to a volume of approximately 10 ml and acidified to pH1 by the addition of 2N aqueous hydrochloric acid solution. The precipitate was filtered off, washed with water and dried. There was thus obtained the required starting material (1.24 g), m.p. 260-262 °C.

45

EXAMPLE 16

The process described in Example 1 was repeated except that 6-aminomethyl-3,4-dihydro-2-methyl-3-pivaloyloxymethylquinazolin-4-one was used in place of 3-aminomethylpyridine. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)benzamide (containing 1 equivalent of water, 96%), m.p. 191-193 °C (Example 16, Compound No. 1).

A mixture of a portion (0.253 g) of the product so obtained, 1N aqueous sodium hydroxide solution (4 ml) and ethanol (12 ml) was stirred at laboratory temperature for 2 hours. The mixture was neutralised by the addition of 1N aqueous hydrochloric acid solution and the precipitate so formed was isolated, washed with water and with acetone and dried. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)benzamide (containing 0.7 equivalents of acetone and 0.8 equivalents of sodium hydroxide, 0.169 g), m.p. 284-294 °C.

NMR Spectrum: (CD₃SOCD₃) 2.34 (s, 6H), 3.17 (s, 1H, C≡CH), 4.32 (s, 2H, CH₂C≡CH), 4.54 (d, 2H, NHCH₂), 4.77 (s, 2H), 6.86-7.97 (m, 10H, aromatic), 8.79 (t, 1H, CONH). (Example 16, Compound No. 2).

The 6-aminomethyl-3,4-dihydro-2-methyl-3-pivaloyloxymethylquinazolin-4-one, used as a starting material, was obtained as follows:-

5 Using the procedures described in the second and third paragraphs of Note (v), in the portion of Example 6 which is concerned with the preparation of starting materials, 6-bromomethyl-3,4-dihydro-2-methyl-3-pivaloyloxymethylquinazolin-4-one was reacted with potassium phthalimide and the resultant phthalimide was treated with hydrazine hydrate. There was thus obtained the required starting material, as its hydrochloride salt, in 75% yield. The salt so formed (5.6 g) was dissolved in water (20 ml) and the
10 solution was basified to pH8 by the addition of 2N aqueous sodium hydroxide solution. The mixture was extracted with ethyl acetate (3 x 30 ml). The combined extracts were dried (MgSO₄) and evaporated. There was thus obtained the required free base starting material (1.04 g).

EXAMPLE 17

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The process described in Example 1 was repeated except that 6-aminomethyl-3,4-dihydro-3-pivaloyloxymethylquinazolin-4-one was used in place of 3-aminomethylpyridine. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)benzamide (48%), m.p. 165-168 °C (Example 17, Compound No. 1).

20 A mixture of the product so obtained (0.18 g), 1N aqueous sodium hydroxide solution (2.3 ml) and ethanol (8 ml) was stirred at laboratory temperature for 16 hours. The bulk of the ethanol was evaporated, water (15 ml) was added and the mixture was acidified to pH5 by the addition of 2N aqueous hydrochloric acid solution. The gelatinous precipitate so formed was isolated by centrifugation, washed with water and dried. The crude product (0.21 g) so obtained was purified by column chromatography on silica gel using
25 increasingly polar mixtures of methylene chloride and ethanol as eluent. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-4-oxoquinazolin-6-ylmethyl)benzamide (containing 0.25 equivalents of water and 1.5 equivalents of sodium hydroxide, 0.066 g), m.p. 192-200 °C.

30 NMR Spectrum (CD₃SOCD₃) 2.37 (s, 3H), 3.18 (s, 1H, C≡CH), 4.32 (s, 2H, CH₂C≡C), 4.57 (d, 2H, NHCH₂), 4.80 (s, 2H, ArCH₂), 6.87 (d, 2H, aromatic), 7.56-8.06 (m, 9H, aromatic), 8.83 (hump, 1H). (Example 17, Compound No. 2).

The 6-aminomethyl-3,4-dihydro-3-pivaloyloxymethylquinazolin-4-one, used as a starting material, was obtained from 6-bromomethyl-3,4-dihydro-3-pivaloyloxymethylquinazolin-4-one (J. Med. Chem., 1989, 32, 847) using the procedure described in Note (x) below Table IV in Example 6 i.e. reaction with sodium azide
35 and reduction of the azide so formed by hydrogenation. The reaction of the 6-bromomethyl derivative was carried out at laboratory temperature for 2.5 hours. The required starting material was obtained in 88% yield, as a white foam.

EXAMPLE 18

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The process described in Example 10 was repeated except that 6-aminomethyl-3,4-dihydro-2,3-dimethylquinazolin-4-one was used in place of 4-fluorobenzylamine. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2,3-dimethyl-4-oxoquinazolin-6-ylmethyl)benzamide (containing 2 equivalents of water, 24%), m.p. 210-211 °C.

45 The 6-aminomethyl-3,4-dihydro-2,3-dimethylquinazolin-4-one, used as a starting material, was obtained from 3,4-dihydro-2,3,6-trimethylquinazolin-4-one, as an oily solid in 25% overall yield, using the procedure described in Note (xiii) below Table IV in Example 6.

EXAMPLE 19

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6-Bromomethyl-3,4-dihydro-2-methylquinazolin-4-one (0.56 g) and 2,6-lutidine (0.35 ml) were added in turn to a solution of N-(3-nitrobenzyl)-5-methylaminothiophene-2-carboxamide (0.43 g) in N-methylpyrrolidin-2-one (5 ml) and the mixture was heated to 90 °C for 4 hours. The mixture was poured into water (50 ml) and the resultant mixture was extracted with ethyl acetate. The organic phase was washed with water, dried
55 (Na₂SO₄) and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate and then a 19:1 v/v mixture of ethyl acetate and methanol as eluent. There was thus obtained 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-N-(3-nitrobenzyl) thiophene-2-carboxamide (0.055 g), m.p. 155-158 °C.

The N-(3-nitrobenzyl)-5-methylaminothiophene-2-carboxamide, used as a starting material, was obtained as follows:-

Triethylamine (2 ml), diphenylphosphoryl azide (2.5 ml) and 3-nitrobenzylamine (1.2 g) were each added in turn to a solution of 5-(N-tert-butoxycarbonyl-N-methylamino)thiophene-2-carboxylic acid (1.25 g) in dimethylformamide (30 ml) and the mixture was stirred at laboratory temperature for 18 hours. The mixture was poured into water (200 ml) and extracted with ethyl acetate (4 x 100 ml). The combined extracts were dried (Na₂SO₄) and evaporated. The residue was purified by column chromatography using a 4:1 v/v mixture of hexane and ethyl acetate as eluent. There was thus obtained 5-(N-tert-butoxycarbonyl-N-methylamino)-N-(3-nitrobenzyl)thiophene-2-carboxamide (1.95 g), as a yellow solid.

A portion (1 g) of the product so obtained was dissolved in trifluoroacetic acid (20 ml) and the solution was stirred at laboratory temperature for 2 hours. The solution was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried (Na₂SO₄) and evaporated. The residue was purified by column chromatography using a 4:1 v/v mixture of hexane and ethyl acetate as eluent. There was thus obtained the required starting material (0.43 g), as an oil.

EXAMPLE 20

The process described in Example 10 was repeated except that 2-[N-(4-hydroxypyrimidin-2-ylamino)-ethyl]amine was used in place of 4-fluorobenzylamine. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-[2-(4-hydroxypyrimidin-2-ylamino)ethyl]benzamide in 80% yield, m.p. > 300 ° C (decomposes).

NMR Spectrum: (CD₃SOCD₃) 2.33 (s, 3H), 3.18 (s, 1H), 3.40 (s, 4H), 4.32 (s, 2H), 4.78 (s, 2H), 5.53 (m, 1H), 6.8-8.2 (m, 9H).

The 2-[N-(4-hydroxypyrimidin-2-ylamino)ethyl]amine, used as a starting material, was obtained as follows:-

A mixture of 4-hydroxy-2-methylthiopyrimidine (18.5 g) and 2-(benzyloxycarbonylamino)ethylamine (27.2 g) was heated to 140 ° C for 2 hours. Ethyl acetate (200 ml) was added and the precipitate was filtered off. There was thus obtained 2-[2-(benzyloxycarbonylamino)ethylamino]-4-hydroxypyrimidine (22.7 g), m.p. 145-146 ° C (recrystallised from isopropanol).

A mixture of a portion (9.8 g) of the product so obtained, ammonium formate (4.3 g), 10% palladium-on-charcoal catalyst (1 g) and methanol (130 ml) was stirred at laboratory temperature for 18 hours. The mixture was filtered and the filtrate was evaporated to give the required starting material.

EXAMPLE 21

The process described in Example 12 was repeated except that 3-aminoglutarimide (J. Amer. Chem. Soc., 1957, 79, 3767) was used in place of 3-aminosuccinimide. The crude reaction product was purified by column chromatography on reversed-phase silica gel (Dynamax) using a 40:60:0.2 v/v mixture of methanol: water: trifluoroacetic acid as eluent. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2, 6-dioxopiperidin-3-yl)benzamide (containing 1.3 equivalents of trifluoroacetic acid, 32%), m.p. 161-168 ° C.

NMR Spectrum: (CD₃SOCD₃) 2.02 (m, 2H), 2.40 (s, 3H), 2.52 (m, 1H), 2.77 (m, 1H), 3.18 (t, 1H), 4.33 (t, 2H), 4.72 (m, 1H), 4.83 (s, 2H), 6.86 (d, 2H), 7.56 (d, 1H), 7.71 (d, 2H), 7.72 (g, 1H), 8.01 (d, 1H), 8.39 (d, 1H), 10.77 (s, 1H);

Mass Spectrum: (positive ion FAB) m/e (P + 1) 458;

Elemental Analysis: Found	C, 54.8;	H, 4.2;	N, 11.4;
C ₂₅ H ₂₃ N ₅ O ₄ . 1.3CF ₃ CO ₂ H requires	C, 54.7;	H, 4.0;	N, 11.6%.

EXAMPLE 22

Using the procedure described in Example 10, p-[N-(3,4-dihydro-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid was reacted with 3-nitrobenzylamine to give p-[N-(3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide (containing 1 equivalent of water, 56%), m.p. 197-199 ° C.

The p-[N-(3,4-dihydro-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, used as a starting material, was obtained by reacting 6-bromomethyl-3,4-dihydro-3-pivaloyloxymethyl-quinazolin-4-one [UK Patent Specification No. 2175903B] with tert-butyl p-(prop-2-ynylamino)benzoate and by treating the resultant product with trifluoroacetic acid. There was thus obtained the required starting material in 53% yield, m.p. 93-96 °C.

EXAMPLE 23

Using the procedure described in Example 10, p-[N-(3,4-dihydro-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid was reacted with 3-aminomethylpyridine to give p-[N-(3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)benzamide (containing 4.5 equivalents of water, 61%), m.p. 137-139 °C.

EXAMPLE 24

The process described in Example 5 was repeated except that N-(cyanomethyl)-N-methylamine was used in place of 3-nitrobenzyl alcohol. The reaction mixture was stirred at laboratory temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and ethanol as eluent. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(cyanomethyl)-N-methylbenzamide (68%), m.p. 214-215 °C, and p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-[3-(hexahydro-2-oxoazepin-1-yl)propyl]benzamide (containing 0.5 equivalents of water; 23%), m.p. 208-210 °C, (this product arising from reaction of the benzoyl azide with 1,8-diazabicyclo[5.4.0]undec-7-ene).

EXAMPLE 25

Using the procedure described in Example 5, p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]benzoyl azide was treated with L-histidine. The mixture was stirred at laboratory temperature for 16 hours. The mixture was evaporated, the residue was dissolved in water and the solution was acidified to pH4 by the addition of 2N aqueous hydrochloric acid. The precipitate so formed was isolated by centrifugation and purified by column chromatography on silica gel using a 9:1 v/v mixture of chloroform and methanol as eluent. There were thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-N-[3-(hexahydro-2-oxoazepin-1-yl)propyl]benzamide (containing 1.8 equivalents of water; 15%), m.p. 155-157 °C, (the product arising from reaction of the benzoyl azide with 1,8-diazabicyclo[5.4.0]undec-7-ene).

EXAMPLE 26

Using the procedure described in Example 10, p-[N-(3,4-dihydro-7-fluoro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid was reacted with 3-nitrobenzylamine. There was thus obtained p-[N-(3,4-dihydro-7-fluoro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide (containing 1.5 equivalents of water, 76%, m.p. 235-237 °C).

The p-[N-(3,4-dihydro-7-fluoro-2-methyl-3-pivaloyloxymethyl 4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, used as a starting material, was obtained as follows:-

3,4-Dihydro-7-fluoro-2,6-dimethylquinazolin-4-one was prepared from 3-fluoro-4-methylacetanilide using the procedure described in UK Patent Specification No. 2202847A for the preparation of 3,4-dihydro-2,6,7-trimethylquinazolin-4-one from 3,4-dimethylacetanilide.

Using the procedure described in the four paragraphs of the portion of Example 10 which is concerned with the preparation of starting materials, the product so obtained was converted in 15% yield to p-[N-(3,4-dihydro-7-fluoro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, m.p. 173-174 °C.

EXAMPLE 27

The procedure described in Example 26 was repeated except that 3-aminomethylpyridine was used in place of 3-nitrobenzylamine. There was thus obtained p-[N-(3,4-dihydro-7-fluoro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)benzamide (containing one equivalent of water), m.p.

251-253 °C.

The procedure described immediately above was repeated except that 3-cyanobenzylamine was used in place of 3-aminomethylpyridine. There was thus obtained N-(3-cyanobenzyl)-p-[N-(3,4-dihydro-7-fluoro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamide (containing 0.75 equivalents of water),
 5 m.p. 232 °C.

EXAMPLE 28

Using the procedure described in Example 10, p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethyl-
 10 quinazolin-6-ylmethyl)-N-(2-acetoxyethyl)amino]benzoic acid was reacted with 3-nitrobenzylamine to give p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(2-hydroxyethyl)amino-N-(3-nitrobenzyl)benzamide (containing 1 equivalent of water) in 46% yield, m.p. 230-232 °C.

The p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)-N-(2-acetoxyethyl)-
 amino]benzoic acid, used as a starting material, was obtained by reacting 6-bromomethyl-3,4-dihydro-3-
 15 pivaloyloxymethylquinazolin-4-one [UK Patent Specification No. 2175903B] with tert-butyl p-(2-acetoxyethylamino)benzoate [prepared by the reaction of tert-butyl p-aminobenzoate with 2-acetoxyethyl bromide, and by treating the resultant product with trifluoroacetic acid]. There was thus obtained the required starting material as a foam.

20 EXAMPLE 29

Using the procedure described in Example 10, p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethyl-
 quinazolin-6-ylmethyl)-N-(2-acetoxyethyl)amino]benzoic acid was reacted with 3-cyanobenzylamine to give
 25 N-(3-cyanobenzyl)-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(2-hydroxyethyl)amino]-
 benzamide, m.p. 110-112 °C, as a foam.

EXAMPLE 30

The procedure described in Example 10 was repeated except that 2-aminomethylquinoxaline was used
 30 in place of 4-fluorobenzylamine. There was thus obtained p-[N-(3,4-dihydro-2-methyl-3-pivaloyloxymethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(quinoxalin-2-ylmethyl)benzamide in 23% yield, m.p. 126 °C.

The 2-aminomethylquinoxaline, used as a starting material, was obtained from 2-bromomethylquinoxaline using the procedure described in Note (2) below Table I in Example 1.

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EXAMPLE 31

Using the procedure described in Example 1, o-amino-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-
 ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid was reacted with 3-nitrobenzylamine to give o-amino-p-[N-(3,4-
 40 dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide in 64%
 yield, m.p. 86-92 °C.

The o-amino-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, used as a starting material, was obtained as follows:-

A mixture of methyl p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino-o-
 45 nitrobenzoate (0.3 g), activated iron powder [1.24 g; activated by stirring a mixture of iron powder and 2N aqueous hydrochloric acid solution for 5 minutes, filtering the mixture and washing the iron with methanol], methanol (10 ml) and concentrated hydrochloric acid (20 drops) was heated to reflux for 80 minutes. The mixture was cooled to laboratory temperature and partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with water, dried and evaporated.
 50 The residue was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained methyl o-amino-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate (0.1 g, 36%).

A mixture of the product so obtained, 1N aqueous sodium hydroxide solution (0.72 ml) and propanol (2 ml) was heated to 80 °C for 30 minutes. The mixture was evaporated, water (2 ml) was added and the
 55 mixture was acidified to pH 3.5 by the addition of 2N aqueous hydrochloric acid solution. The precipitate was isolated by centrifugation and dried. There was thus obtained the required starting material (0.9 g, 94%).

EXAMPLE 32

The procedure described in Example 5 was repeated except that 3-aminomethylpyridine-N-oxide (J. Med. Chem., 1987, 30, 2222) was used in place of 3-nitrobenzyl alcohol. The reaction mixture was evaporated, the residue was dissolved in water and the solution was acidified to pH5 by the addition of 2N aqueous hydrochloric acid solution. The precipitate was filtered off, dried and purified by column chromatography using increasingly polar mixtures of methylene chloride and ethanol as eluent. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(N-oxido-3-ylmethyl)benzamide (0.60 g, 66%), m.p. 170-171 °C.

EXAMPLE 33

A mixture of pentafluorophenyl p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate (0.2 g), 4-aminomethyl-2-hydroxypyridine (0.081 g), triethylamine (0.19 ml), N-hydroxybenzotriazole (1 drop) and dimethylformamide (40 ml) was stirred at laboratory temperature for 16 hours. The mixture was evaporated and the residue was triturated in diethyl ether. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-hydroxypyrid-4-ylmethyl)benzamide in quantitative yield, m.p. 145 °C.

A mixture of the product so obtained, a saturated aqueous ammonium hydroxide solution (7.4 ml) and methanol (15 ml) was stirred at laboratory temperature for 16 hours. The mixture was concentrated by evaporation of the methanol. The precipitate was filtered off and dried. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-hydroxypyrid-4-ylmethyl)benzamide (0.14 g), as a white solid.

NMR Spectrum (CD₃SOCD₃) 2.33 (s, 3H), 3.18 (s, 1H), 4.23 (d, 2H), 4.32 (broad s, 2H), 4.78 (s, 2H), 6.09 (d, 1H), 6.13 (s, 1H), 6.87 (d, 2H), 7.27 (d, 1H), 7.53 (d, 1H), 7.5 (d of d's, 1H), 7.76 (d, 2H), 7.97 (s, 1H), 8.63 (broad s, 1H), 11.32 (broad s, 1H), 12.13 (broad s, 1H).

The pentafluorophenyl p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoate, used as a starting material, was obtained as follows:-

Dicyclohexylcarbodiimide (6.18 g), was added to a suspension of p-[N-(3,4-dihydro-2-methyl-4-oxo-3-pivaloyloxymethylquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid (13.83 g) and pentafluorophenol (5.52 g) in ethyl acetate (450 ml) and the mixture was stirred at laboratory temperature for 18 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica gel using a 1:1 v/v mixture of hexane and ethyl acetate as eluent. There was thus obtained the required starting material (13.9 g), m.p. 143-144 °C.

The 4-aminomethyl-2-hydroxypyridine, used as a starting material, was obtained as follows:-

A mixture of 2-chloro-4-cyanopyridine (7.7 g), platinum dioxide (1.1 g), acetic anhydride (77 ml) and acetic acid (77 ml) was stirred at laboratory temperature under an atmosphere of hydrogen for five hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained 4-acetamidomethyl-2-chloropyridine (2.4 g), m.p. 83 °C.

A mixture of a portion (1.6 g) of the product so obtained and concentrated hydrochloric acid (20 ml) was heated to reflux for four days. The mixture was evaporated to give the required starting material (1.1 g, recrystallised from ethanol).

NMR Spectrum (CD₃SOCD₃) 3.89 (q, 2H), 6.42 (d, 1H), 6.52 (s, 1H), 7.49 (d, 1H), 8.68 (broad s, 3H).

EXAMPLE 34

The procedure described in Example 33 was repeated except that 3-aminomethyl-6-hydroxypyridine was used in place of 4-aminomethyl-2-hydroxypyridine. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(6-hydroxypyrid-3-ylmethyl)benzamide in 64% yield, m.p. 258 °C.

The 3-aminomethyl-6-hydroxypyridine, used as a starting material, was obtained from 3-cyano-6-methoxypyridine using the procedure described in the portion of Example 33 which is concerned with the preparation of 4-aminomethyl-2-hydroxypyridine except that, in the second step described therein, 48% aqueous hydrobromic acid was used in place of concentrated hydrochloric acid. There was thus obtained the required starting material, as the hydrobromide salt, m.p. 239 °C.

EXAMPLE 35

The procedure described in Example 5 was repeated except that 4-aminomethylpiperidine was used in place of 3-nitrobenzyl alcohol to give p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(piperidin-4-ylmethyl)benzamide (containing 3.5 equivalents of water), m.p. 130-133 °C (decomposes).

EXAMPLE 36

The procedure described in Example 5 was repeated except that 2-aminomethyl-N-ethylpyrrolidine was used in place of 3-nitrobenzyl alcohol. There was thus obtained p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(N-ethylpyrrolidin-2-ylmethyl)benzamide (containing 1.3 equivalents of water), m.p. 139-143 °C (decomposes).

EXAMPLE 37

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d)

EP 0 373 891 B1

Capsule	mg/capsule
Compound X	10 mg
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f)

Injection II	(10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g)

Injection III	(1mg/ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a) to (c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CHEMICAL FORMULAE

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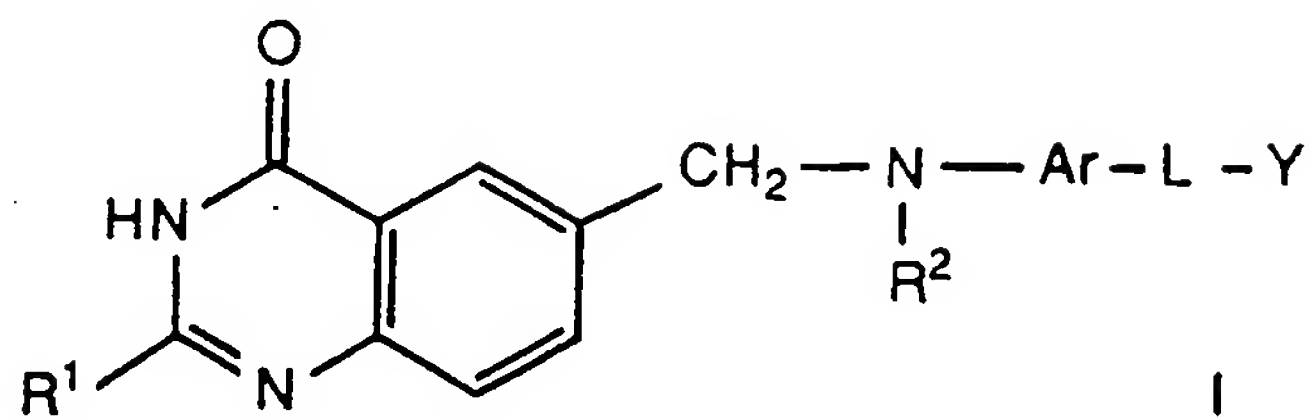
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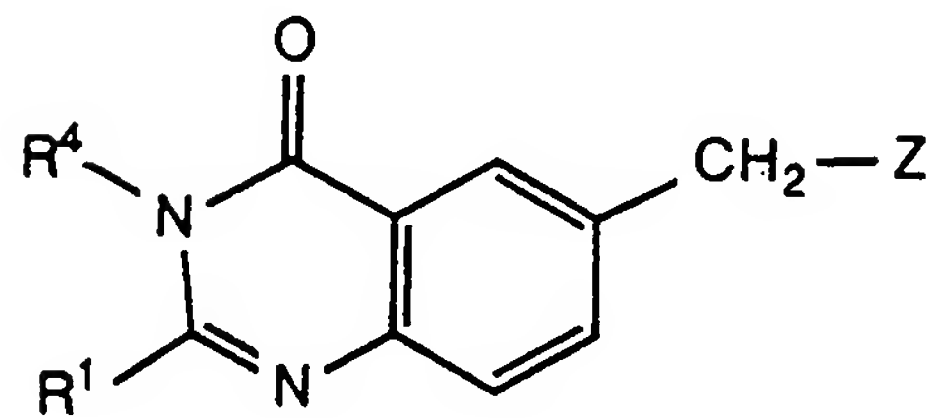
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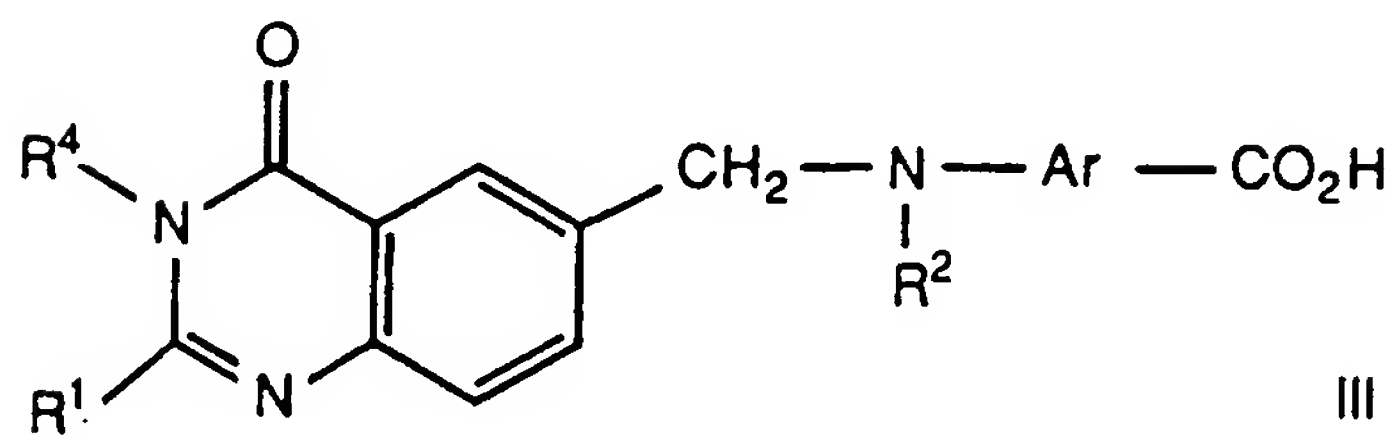
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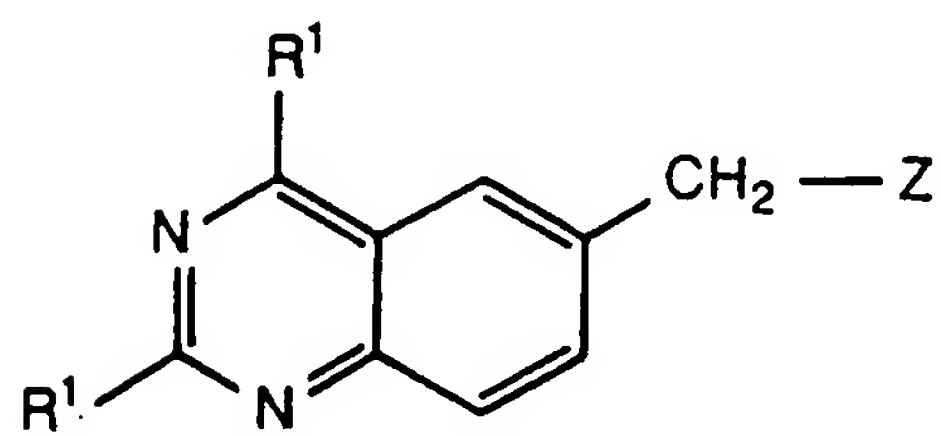
I



II



III

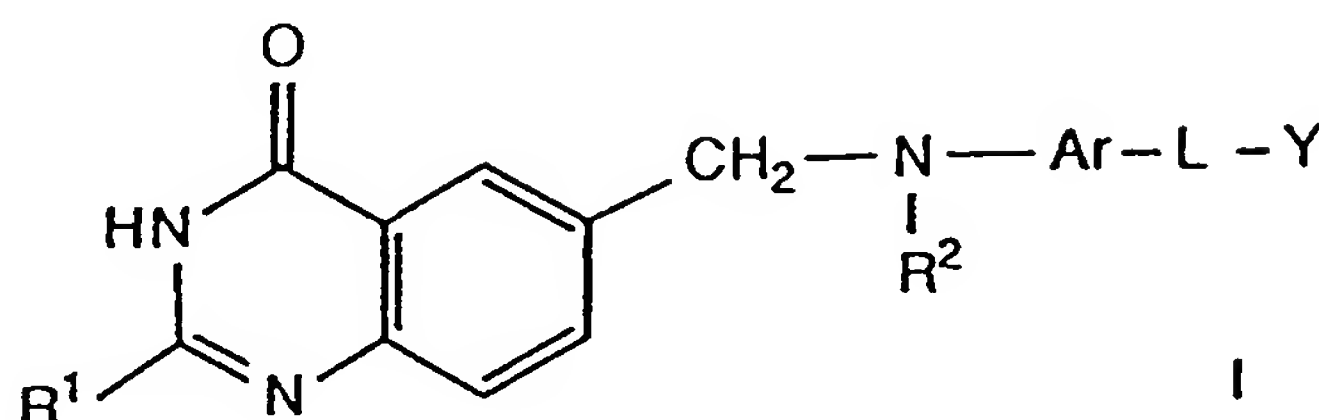


IV

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

1. A quinazoline of the formula I



wherein R¹ is hydrogen or amino, or alkyl or alkoxy each of up to 6 carbon atoms;
 or R¹ is alkyl of up to 3 carbon atoms which bears a hydroxy substituent, or which bears one, two or three fluoro substituents;
 or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms;
 wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from halogeno and from all and alkoxy each of up to 3 carbon atoms;
 wherein R² is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, halogenoalkyl or cyanoalkyl each of up to 6 carbon atoms;
 wherein Ar is phenylene or heterocyclene which may be unsubstituted or may bear one or two substituents selected from halogeno, hydroxy, amino and nitro, and from alkyl, alkoxy and halogenoalkyl each of up to 3 carbon atoms;
 wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-, wherein R³ is alkyl of up to 6 carbon atoms;
 and wherein Y is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; or Y is a group of the formula -A-Y¹ in which A is alkylene, cycloalkylene, alkenylene or alkynylene each of up to 6 carbon atoms, and Y¹ is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group or an alkylimino group of up to 6 carbon atoms;
 and wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy and halogeno, from alkyl, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxycarbonyl, alkanoyloxyalkyl, alkylthio, alkylsulphinyl, alkylsulphonyl, alkoxy, halogenoalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, carbamoylalkyl, N-alkylcarbamoylalkyl and N,N-dialkylcarbamoylalkyl each of up to 6 carbon atoms and from phenyl, pyridyl and phenylalkyl of up to 10 carbon atoms, and wherein each of said phenyl or phenylalkyl groups may bear a substituent selected from halogeno and nitro, and from alkyl and alkoxy each of up to 3 carbon atoms;
 or a pharmaceutically-acceptable salt thereof;
 provided that when R¹ is hydrogen or amino, or alkyl of up to 6 carbon atoms, and L is a group of the formula -CONH-, then Y is not tetrazolyl.

2. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is hydrogen or amino, or methyl, ethyl, methoxy or fluoromethyl;
 wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;
 wherein R² is methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;
 wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene or thiazolylene which is unsubstituted or which bears a substituent selected from fluoro, chloro, bromo, hydroxy, amino, nitro, methyl, methoxy and trifluoromethyl;
 wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and Y is phenyl, 2,5-dioxopyrrolidinyl or 2,6-dioxopiperidinyl, or Y is a group of the formula -A-Y¹ in which A

is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, butylidene, isobutylidene or tetramethylene and Y¹ is phenyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, quinazolinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl or hexahydro-2-oxazepin-1-yl;

5 wherein one constituent methylene group in A may be replaced by a thio, sulphinyl, sulphonyl or imino group; and

wherein each of said phenyl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy, fluoro, chloro, bromo, methyl, ethyl, methylamino, ethylamino, 10 dimethylamino, diethylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, isobutyryloxymethyl, pivaloyloxymethyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, methoxy, ethoxy, trifluoromethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, phenyl, pyridyl, 15 benzyl, phenethyl or phenylpropyl, and wherein any phenyl group within said substituents may bear a substituent selected from fluoro, chloro, bromo, nitro, methyl, ethyl, methoxy and ethoxy; or a pharmaceutically-acceptable salt thereof.

20 3. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is amino, methyl, methoxy or fluoromethyl;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;

wherein R² is methyl, ethyl, prop-2-enyl or prop-2-ynyl;

25 wherein Ar is 1,4-phenylene, thienylene, pyridylene or thiazolylene which is unsubstituted or which bears a fluoro or nitro substituent;

wherein L is a group of the formula -CO.NH- or -CO. O-; and

30 Y is phenyl, or Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene or isobutylidene and Y¹ is phenyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-quinolyl, 4-quinolyl, 8-quinolyl, 2-pyrimidinyl, 4-pyrimidinyl, 6-quinazolinyl, 3-indolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl, 2-thiazolyl, 5-thiazolyl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl or tetrazol-5-yl, or Y is phenylsulphonyl; and

35 wherein each of said phenyl or heteroaryl groups may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, carboxy, fluoro, chloro, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, pivaloyloxymethyl, methoxy, trifluoromethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, 4-pyridyl and benzyl;

or a pharmaceutically-acceptable salt thereof.

40 4. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is amino, methyl or methoxy;

wherein the quinazoline ring may bear a methyl substituent in the 7-position;

wherein R² is methyl, ethyl or prop-2-ynyl;

wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl with the group -L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

45 wherein L is a group of the formula -CONH-;

and wherein Y is benzyl or phenylsulphonyl which may bear a nitro, cyano, carboxy or trifluoromethyl substituent, or Y is thiazol-5-ylmethyl or 1,2,3,6-tetrahydro-2,6-dioxypyrimidin-4-ylmethyl, or Y is 2,3-dihydro-4-oxoquinazolin-6-ylmethyl which may bear one or two methyl substituents;

or a pharmaceutically-acceptable salt thereof;

50 5. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is methyl; wherein the quinazoline ring may bear a methyl substituent in the 7-position; wherein R² is methyl or prop-2-ynyl;

wherein Ar is 1,4-phenylene, or 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

wherein L is a group of the formula -CO.NH-; and

55 Y is a group of the formula -A-Y¹ in which A is methylene and Y is 2-nitrophenyl, 3-nitrophenyl, 3-cyanophenyl, 4-carboxyphenyl or 3-trifluoromethylphenyl, or Y¹ is 5-thiazolyl, 2,3-dihydro-4-oxoquinazolin-6-yl, 2,3-dihydro-2-methyl-4-oxoquinazolin-6-yl or 2,3-dihydro-2,3-dimethyl-4-oxoquinazolin-6-yl;

or a pharmaceutically-acceptable salt thereof.

6. A quinazoline of the Formula I as claimed in claim 1 selected from the group of compounds:-
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-trifluoromethylbenzyl)benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-o-fluoro-N-(3-nitrobenzyl)benzamide;
5 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide;
p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;
p-[N-(2-amino-3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;
10 p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)benzamide and
p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;
15 or a pharmaceutically-acceptable salt thereof.
7. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is alkyl or alkoxy each of up to 6 carbon atoms;
or R¹ is alkyl of up to 3 carbon atoms which bears a hydroxy substituent, or which bears one, two or
25 three fluoro substituents;
or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms;
wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from halogeno and from alkyl and alkoxy each of up to 3 carbon atoms;
wherein R² is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, halogenoalkyl or cyanoalkyl each of up to
30 6 carbon atoms;
wherein Ar is phenylene or heterocyclene which may be unsubstituted or may bear one or two substituents selected from halogeno, hydroxy and amino, and from alkyl, alkoxy and halogenoalkyl each of up to 3 carbon atoms;
wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-,
35 -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-, wherein R³ is alkyl of up to 6 carbon atoms;
and wherein Y is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; or
Y is a group of the formula -A-Y¹ in which A is alkylene, cycloalkylene, alkenylene or alkynylene each of up to 6 carbon atoms, and Y¹ is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof;
40 wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group or an alkylimino group of up to 6 carbon atoms;
and wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy and halogeno, from alkyl, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxy, halogenoalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxyalkyl, carbamoylalkyl, N-alkylcarbamoylalkyl and N,N-dialkylcarbamoylalkyl each of up to 6 carbon atoms and from phenyl and phenylalkyl of up to 10 carbon atoms, and wherein each of said phenyl groups may bear a substituent selected from halogeno and from alkyl and alkoxy each of up to 3 carbon atoms;
45 or a pharmaceutically-acceptable salt thereof;
provided that when R¹ is alkyl of up to 6 carbon atoms, the quinazoline ring bears no further substituents or bears one further substituent selected from halogeno and alkyl of up to 3 carbon atoms, R² is alkyl, alkenyl or alkynyl each of up to 6 carbon atoms,
Ar is phenylene which is unsubstituted or bears one or two substituents selected from halogeno,
50 hydroxy and amino, and
L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.

8. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is methyl, ethyl, methoxy or fluoromethyl;
 wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;
 5 wherein R² is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;
 wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene, thiazolylene or thiadiazolylene which is unsubstituted or which bears one or two substituents selected from fluoro, chloro, bromo, hydroxy, amino, methyl, methoxy and trifluoromethyl;
 10 wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.HR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -CO.CH₂- or -CO.O-, wherein R³ is methyl or ethyl; and
 Y is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl; or
 Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, 1-isopropylethylene or tetramethylene and Y¹ is phenyl, naphthyl, pyridyl,
 15 quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl;
 wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl or sulphonyl group; and
 20 wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy, fluoro, chloro, bromo, methyl, ethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, isopropylsulphinyl, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, methoxy, ethoxy, trifluoromethyl, carboxymethyl, 2-carboxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, phenyl, benzyl, phenethyl or phenylpropyl, and wherein each of said phenyl groups may bear a substituent selected from fluoro, chloro, bromo, methyl, ethyl, methoxy and ethoxy;
 25 or a pharmaceutically acceptable salt thereof;
 30 provided that when R¹ is methyl or ethyl, the quinazoline ring bears no further substituents or bears one further substituent selected from fluoro, chloro and methyl,
 R² is methyl, ethyl, propyl, prop-2-enyl or prop-2-ynyl,
 Ar is 1,4-phenylene which is unsubstituted or bears one or two substituents selected from fluoro, chloro, bromo, hydroxy and amino, and
 35 L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.
9. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is methyl, ethyl, methoxy or fluoromethyl;
 wherein the quinazoline ring may bear no further substituents or may bear one further substituent
 40 selected from fluoro, chloro, methyl and methoxy;
 wherein R² is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;
 wherein Ar is 1,4-phenylene, thien-2,5-diyl, pyrid-2,5-diyl or thiazol-2,5-diyl which is unsubstituted or which bears one or two substituents selected from fluoro, chloro, hydroxy, amino and methyl;
 45 wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and
 Y is phenyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl or 1,2,3-triazolyl; or
 Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene or trimethylene and Y¹ is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl; and
 50 wherein each of said aryl or heteroaryl groups may be unsubstituted or may bear one or two substituents selected from amino, nitro, fluoro, methyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, methylsulphinyl, methylsulphonyl, methoxy, trifluoromethyl or benzyl;
 or a pharmaceutically-acceptable salt thereof.
- 55 10. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is methyl; wherein R² is hydrogen, methyl, ethyl, prop-2-ynyl or 2-fluoroethyl;
 wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl or thiazol-2,5-diyl each with the group

-L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;
wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and
wherein Y is phenyl; or

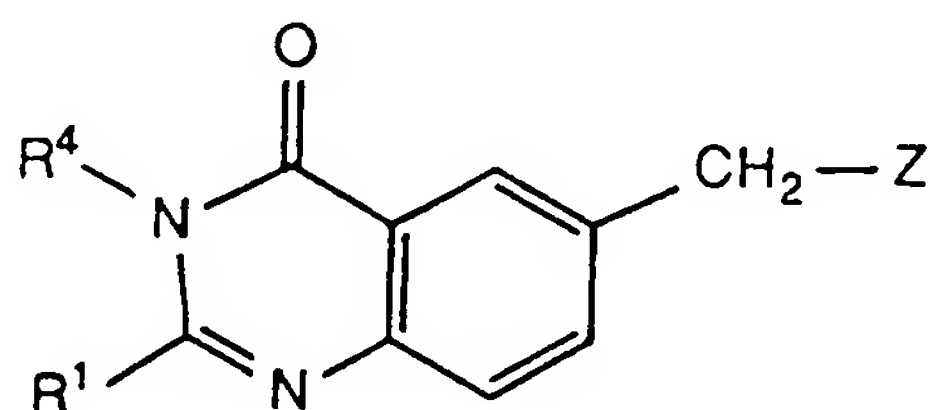
Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene or trimethylene and Y¹
is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-pyrimidinyl, 4-
pyrimidinyl, 5-pyrimidinyl, 2-indolyl, 3-indolyl, 1-imidazolyl, 2-imidazolyl, 2-benzimidazolyl, 1-pyrazolyl,
3-pyrazolyl, 4-pyrazolyl, 3-indazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-
yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-1-yl, 2-thiadiazolyl or 5-tetrazolyl; and
wherein each of said aryl or heteroaryl groups may be unsubstituted or may bear one or two
substituents selected from amino, nitro, carbamoyl, fluoro, methyl, ethoxycarbonyl, methylsulphinyl,
methylsulphonyl, methoxy, trifluoromethyl or benzyl;
or a pharmaceutically-acceptable salt thereof.

11. A quinazoline of the formula I as claimed in claim 1 wherein R¹ is methyl; wherein R² is methyl, ethyl or
prop-2-ynyl;
wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl or thiazol-2,5-diyl each with the group
-L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;
wherein L is a group of the formula -CO.NH- and
Y is a group of the formula -A-Y¹ in which A is methylene or ethylene and Y¹ is 2-pyridyl, 3-pyridyl, 4-
pyridyl, 3-indolyl or 1,2,4-triazol-1-yl, or Y¹ is phenyl which may be unsubstituted or may bear a
substituent selected from amino, nitro, ethoxycarbonyl or trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

12. A quinazoline of the Formula I as claimed in claim 1 selected from the group of compounds:-
N-benzyl-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)-
benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylmethyl)-
benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)-
benzamide and
N-benzylimidazol-2-ylmethyl p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]-
benzoate.

13. A process for the manufacture of a quinazoline as claimed in any one of claims 1 to 12 which
comprises:-

(a) the reaction of a compound of the formula II



II

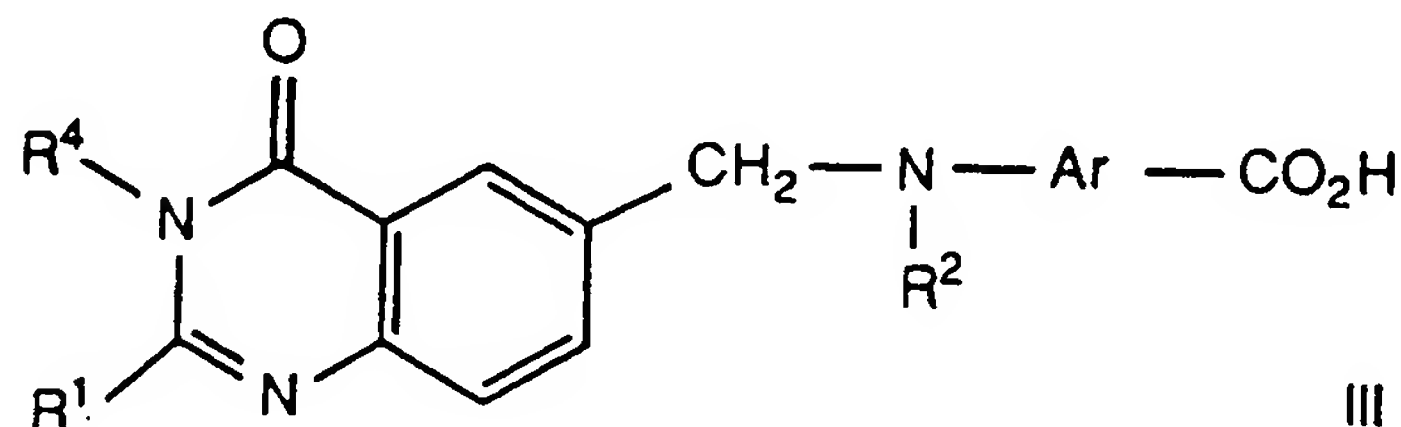
wherein R¹ has the meaning stated in claim 1, provided that when R¹ is amino, hydroxyalkyl or
hydroxyalkoxy any amino or hydroxy group is protected by a conventional protecting group, R⁴ is
hydrogen or a protecting group and Z is a displaceable group, with a compound of the formula:-

HNR²-Ar-L-Y

wherein R², Ar, L and Y have the meanings stated in claim 1, provided that when there is an amino,
alkylamino, imino, hydroxy or carboxy group in R², Ar or Y, any amino, alkylamino, imino and
carboxy group is protected by a conventional protecting group and any hydroxy group may be
protected by a conventional protecting group or alternatively any hydroxy group need not be
protected ;

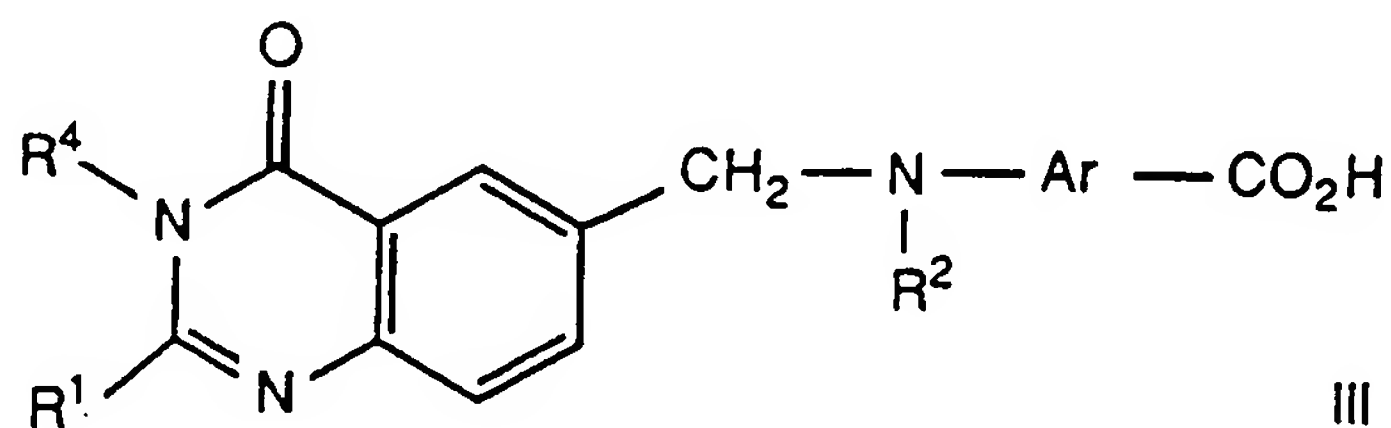
whereafter any undesired protecting group in R^1 , R^2 , Ar and Y is removed;

(b) for the manufacture of a quinazoline as claimed in claim 1 wherein L is a group of the formula -CONH- or -CONR³-, the reaction of an acid of the formula III, or a reactive derivative thereof,



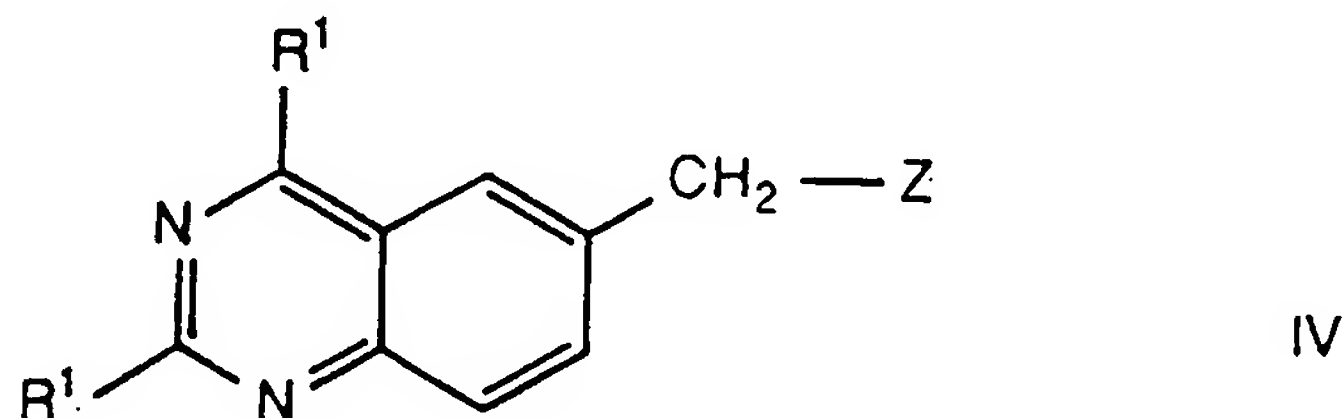
15 with a compound of the formula H_2N-Y or R^3NH-Y wherein R^1 , R^2 , R^3 , R^4 , Ar and Y have the meanings stated in claim 1 and any amino, alkylamino, imino and carboxy group in R^1 , Ar and Y is protected by a conventional protecting group and any hydroxy group in R^1 , R^2 , Ar and Y may be protected by a conventional protecting group or alternatively any hydroxy group need not be protected; whereafter the protecting groups are removed by conventional means;

20 (c) for the manufacture of a quinazoline as claimed in claim 1 wherein L is a group of the formula -CO.O-, the reaction, in the presence of a suitable base, of an acid of the formula III, or a reactive derivative thereof,

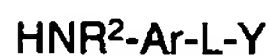


35 with a compound of the formula $HO-Y$, wherein R^1 , R^2 , R^3 , R^4 , Ar and Y have the meanings stated in claim 1 and any amino, alkylamino, imino, hydroxy and carboxy group in R^1 , R^2 , Ar and Y is protected by a conventional protecting group; whereafter the protecting groups are removed by conventional means;

(d) for the manufacture of a quinazoline as claimed in claim 1, wherein R^1 is alkoxy, hydroxyalkoxy or alkoxyalkoxy, the reaction of a compound of the formula IV



50 wherein R^1 has the last-mentioned meaning stated above, provided that when there is a hydroxy substituent in R^1 it is protected by a conventional protecting group, and Z is a displaceable group, with a compound of the formula:



wherein R^2 , Ar, L and Y have the meanings stated in claim 1, provided that when there is an amino, alkylamino, imino, hydroxy or carboxy group in R^2 , Ar or Y any amino, alkylamino, imino and carboxy group is protected by a conventional protecting group and any hydroxy group may be

protected by a conventional protecting group, or alternatively any hydroxy group need not be protected;

whereafter the protecting groups are removed by conventional means, and the R¹ group situated at the 4-position of the quinazoline ring is cleaved by hydrolysis with a base;

(e) for the manufacture of a quinazoline as claimed in claim 1 wherein Y is a group of the formula -A-Y¹ in which one constituent methylene group in A is replaced by a sulphinyl or sulphonyl group, or wherein there is an alkylsulphinyl or alkylsulphonyl substituent in Y, the oxidation of a compound of the formula I wherein Y is a group of the formula -A-Y¹ in which A is replaced by a thio group, or wherein there is an alkylthio substituent in Y; and

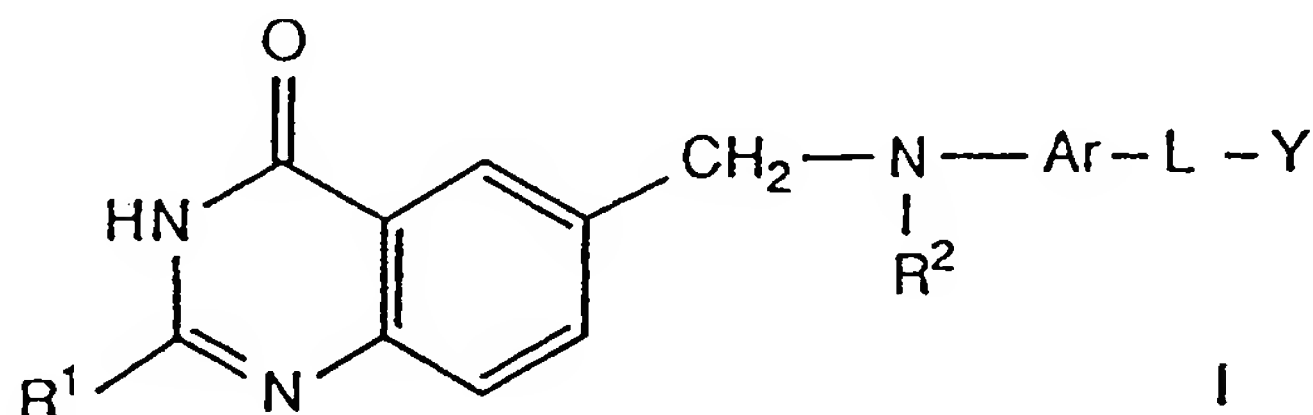
(f) for the manufacture of a quinazoline as claimed in claim 1 wherein there is a carboxy or carboxyalkyl substituent in Y, the cleavage of a compound of the formula I wherein there is an alkoxycarbonyl or alkoxycarbonylalkyl substituent in Y.

14. A pharmaceutical composition which comprises a quinazoline as claimed in claim 1, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

15. The use of a quinazoline as claimed in claim 1, or a pharmaceutically-acceptable salt thereof, in the manufacture of a novel medicament for use in the production of an anti-tumour effect in a warm blooded animal such as man.

Claims for the following Contracting States : GR, ES

1. A process for the manufacture of a quinazoline of the formula I



wherein R¹ is hydrogen or amino, or all or alkoxy each of up to 6 carbon atoms; or R¹ is alkyl of up to 3 carbon atoms which bears a hydroxy substituent, or which bears one, two or three fluoro substituents;

or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from halogeno and from all and alkoxy each of up to 3 carbon atoms;

wherein R² is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, halogenoalkyl or cyanoalkyl each of up to 6 carbon atoms;

wherein Ar is phenylene or heterocyclene which may be unsubstituted or may bear one or two substituents selected from halogeno, hydroxy, amino and nitro, and from alkyl, alkoxy and halogenoalkyl each of up to 3 carbon atoms;

wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-, wherein R³ is all of up to 6 carbon atoms; and

wherein Y is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; or

Y is a group of the formula -A-Y¹ in which A is alkylene, cycloalkylene, alkenylene or alkynylene each of up to 6 carbon atoms, and Y¹ is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof;

wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group or an alkylimino group of up to 6 carbon atoms;

and wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy and halogeno, from alkyl, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxycarbonyl, alkanoyloxyalkyl, alkylthio, alkylsulphinyl, alkylsulphonyl, alkoxy, halogenoalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycar-

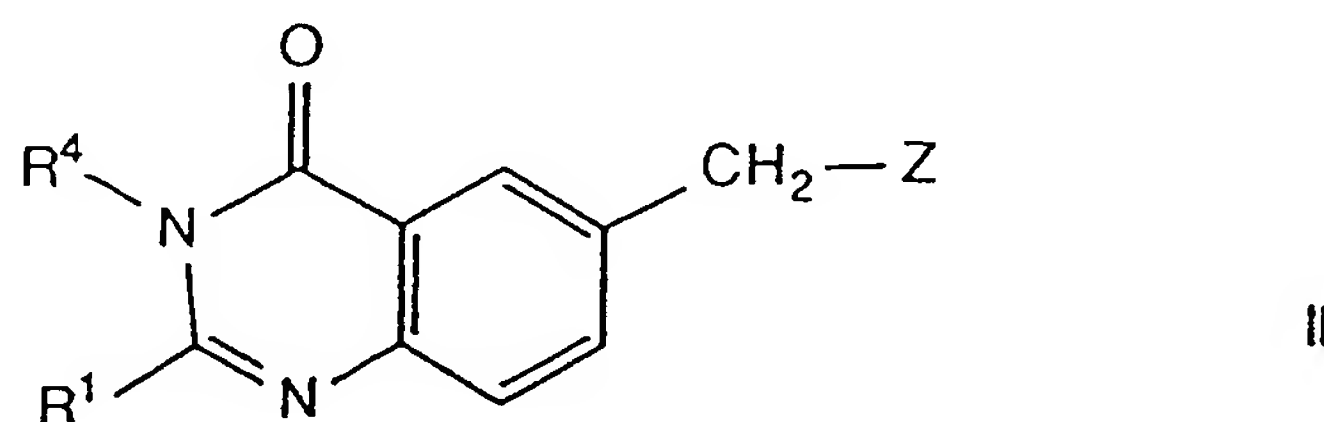
bonylalkyl, carbamoylalkyl, N-alkylcarbamoylalkyl and N,N-dialkylcarbamoylalkyl each of up to 6 carbon atoms and from phenyl, pyridyl and phenylalkyl of up to 10 carbon atoms, and wherein each of said phenyl or phenylalkyl groups may bear a substituent selected from halogeno and nitro, and from alkyl and alkoxy each of up to 3 carbon atoms;

or a pharmaceutically-acceptable salt thereof;

provided that when R¹ is hydrogen or amino, or alkyl of up to 6 carbon atoms, and L is a group of the formula -CONH-, then Y is not tetrazolyl;

characterised by:-

(a) the reaction of a compound of the formula II



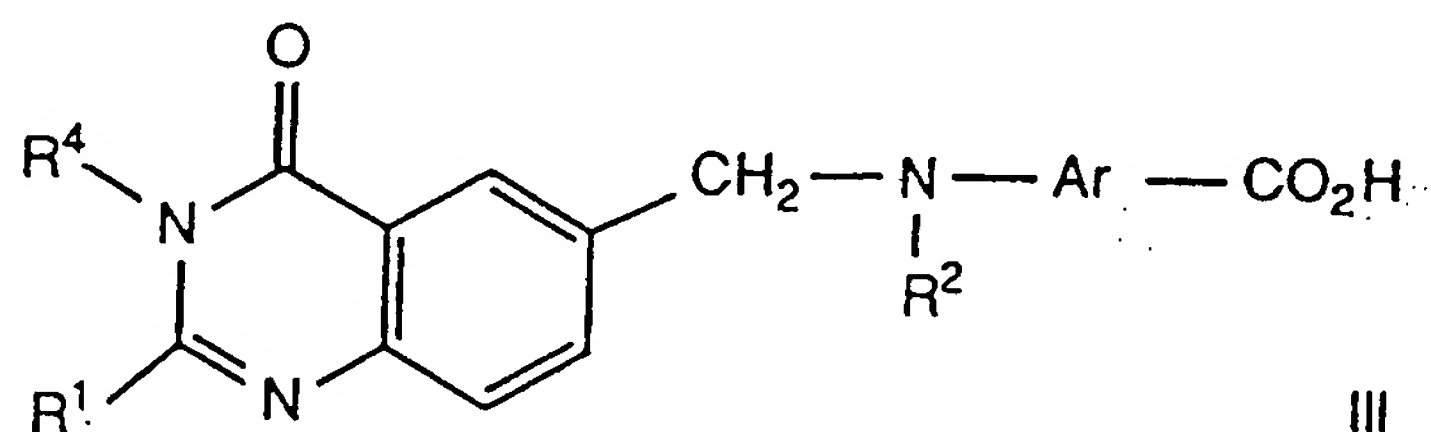
wherein R¹ has the meaning stated above, provided that when R¹ is amino, hydroxyalkyl or hydroxyalkoxy any amino or hydroxy group is protected by a conventional protecting group, R⁴ is hydrogen or a protecting group and Z is a displaceable group, with a compound of the formula:-

HNR²-Ar-L-Y

wherein R², Ar, L and Y have the meanings stated above, provided that when there is an amino, alkylamino, imino, hydroxy or carboxy group in R², Ar or Y, any amino, alkylamino, imino and carboxy group is protected by a conventional protecting group and any hydroxy group may be protected by a conventional protecting group or alternatively any hydroxy group need not be protected ;

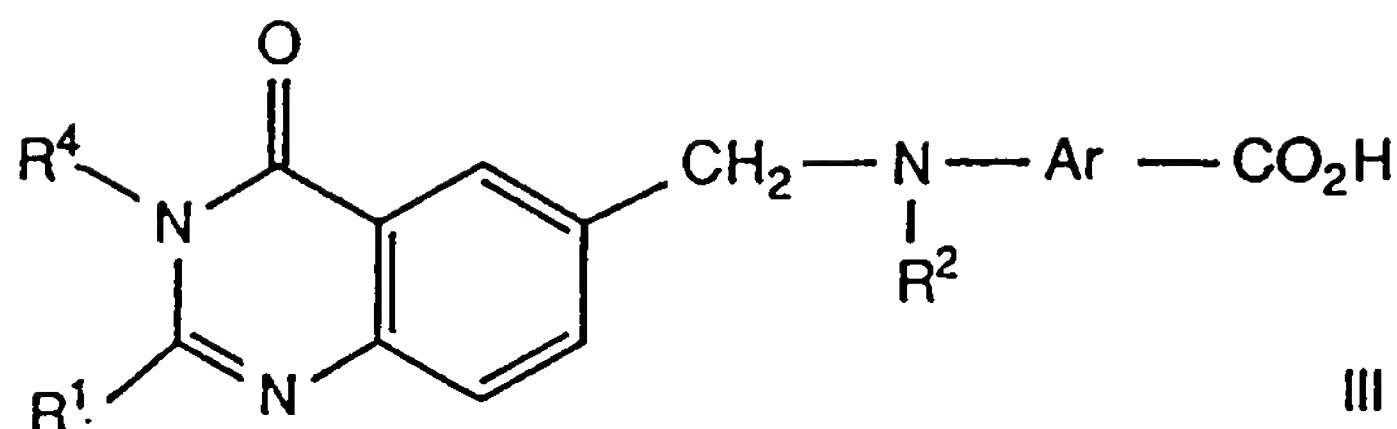
whereafter any undesired protecting group in R¹, R², Ar and Y is removed;

(b) for the manufacture of a quinazoline of the formula I wherein L is a group of the formula -CONH- or -CONR³-, the reaction of an acid of the formula III, or a reactive derivative thereof,



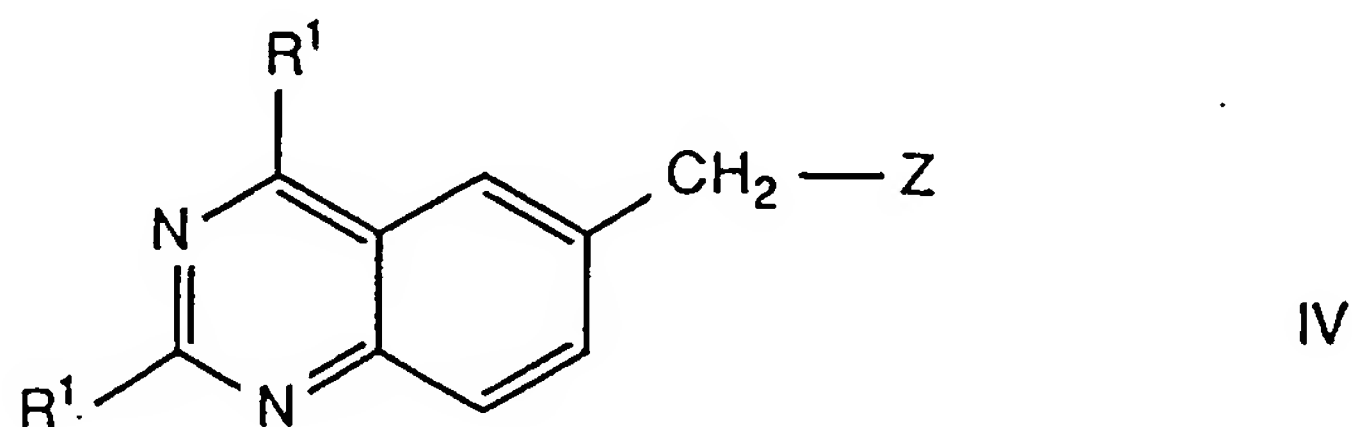
with a compound of the formula H₂N-Y or R³NH-Y wherein R¹, R², R³, R⁴, Ar and Y have the meanings stated above and any amino, alkylamino, imino and carboxy group in R¹, Ar and Y is protected by a conventional protecting group and any hydroxy group in R¹, R², Ar and Y may be protected by a conventional protecting group or alternatively any hydroxy group need not be protected; whereafter the protecting groups are removed by conventional means;

(c) for the manufacture of a quinazoline of the formula I wherein L is a group of the formula -CO.O-, the reaction, in the presence of a suitable base, of an acid of the formula III, or a reactive derivative thereof,

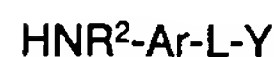


with a compound of the formula HO-Y, wherein R¹, R², R³, R⁴, Ar and Y have the meanings stated above and any amino, alkylamino, imino, hydroxy and carboxy group in R¹, R², Ar and Y is protected by a conventional protecting group; whereafter the protecting groups are removed by conventional means;

(d) for the manufacture of a quinazoline of the formula I, wherein R¹ is alkoxy, hydroxyalkoxy or alkoxyalkoxy, the reaction of a compound of the formula IV



wherein R¹ has the last-mentioned meaning stated above, provided that when there is a hydroxy substituent in R¹ it is protected by a conventional protecting group, and Z is a displaceable group, with a compound of the formula:



wherein R², Ar, L and Y have the meanings stated above, provided that when there is an amino, alkylamino, imino, hydroxy or carboxy group in R², Ar or Y any amino, alkylamino, imino and carboxy group is protected by a conventional protecting group and any hydroxy group may be protected by a conventional protecting group, or alternatively any hydroxy group need not be protected;

whereafter the protecting groups are removed by conventional means, and the R¹ group situated at the 4-position of the quinazoline ring is cleaved by hydrolysis with a base;

(e) for the manufacture of a quinazoline of the formula I wherein Y is a group of the formula -A-Y¹ in which one constituent methylene group in A is replaced by a sulphinyl or sulphonyl group, or wherein there is an alkylsulphinyl or alkylsulphonyl substituent in Y, the oxidation of a compound of the formula I wherein Y is a group of the formula -A-Y¹ in which A is replaced by a thio group, or wherein there is an alkylthio substituent in Y; and

(f) for the manufacture of a quinazoline of the formula I wherein there is a carboxy or carboxyalkyl substituent in Y, the cleavage of a compound of the formula I wherein there is an alkoxycarbonyl or alkoxycarbonylalkyl substituent in Y.

2. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is hydrogen or amino, or methyl, ethyl, methoxy or fluoromethyl;
- wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;
- wherein R² is methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;
- wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene or thiazolylene which is unsubstituted or which bears a substituent selected from fluoro, chloro, bromo, hydroxy, amino, nitro, methyl, methoxy and trifluoromethyl;

wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and Y is phenyl, 2,5-dioxopyrrolidinyl or 2,6-dioxopiperidinyl, or Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, butylidene, isobutylidene or tetramethylene and Y¹ is phenyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, quinazolinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl or hexahydro-2-oxazepin-1-yl;

wherein one constituent methylene group in A may be replaced by a thio, sulphinyl, sulphonyl or imino group; and

wherein each of said phenyl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, sulphamoyl, carboxy, fluoro, chloro, bromo, methyl, ethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, isobutyryloxymethyl, pivaloyloxymethyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, methoxy, ethoxy, trifluoromethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, phenyl, pyridyl, benzyl, phenethyl or phenylpropyl, and wherein any phenyl group within said substituents may bear a substituent selected from fluoro, chloro, bromo, nitro, methyl, ethyl, methoxy and ethoxy; or a pharmaceutically-acceptable salt thereof.

3. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is amino, methyl, methoxy or fluoromethyl;

wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;

wherein R² is methyl, ethyl, prop-2-enyl or prop-2-ynyl;

wherein Ar is 1,4-phenylene, thienylene, pyridylene or thiazolylene which is unsubstituted or which bears a fluoro or nitro substituent; wherein L is a group of the formula -CO.NH- or -CO.O-; and

Y is phenyl, or Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene or isobutylidene and Y¹ is phenyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-quinolyl, 4-quinolyl, 8-quinolyl, 2-pyrimidinyl, 4-pyrimidinyl, 6-quinazolinyl, 3-indolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl, 2-thiazolyl, 5-thiazolyl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl or tetrazol-5-yl, or Y is phenylsulphonyl; and

wherein each of said phenyl or heteroaryl groups may be unsubstituted or may bear up to three substituents selected from hydroxy, oxo, amino, nitro, cyano, carbamoyl, carboxy, fluoro, chloro, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, pivaloyloxymethyl, methoxy, trifluoromethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, 4-pyridyl and benzyl;

or a pharmaceutically-acceptable salt thereof.

4. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is amino, methyl or methoxy; wherein the quinazoline ring may bear a methyl substituent in the 7-position; wherein R² is methyl, ethyl or prop-2-ynyl;

wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl with the group -L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

wherein L is a group of the formula -CONH-;

and wherein Y is benzyl or phenylsulphonyl which may bear a nitro, cyano, carboxy or trifluoromethyl substituent, or Y is thiazol-5-ylmethyl or 1,2,3,6-tetrahydro-2,6-dioxypyrimidin-4-ylmethyl, or Y is 2,3-dihydro-4-oxoquinazolin-6-ylmethyl which may bear one or two methyl substituents;

or a pharmaceutically-acceptable salt thereof;

5. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is methyl; wherein the quinazoline ring may bear a methyl substituent in the 7-position; wherein R² is methyl or prop-2-ynyl; wherein Ar is 1,4-phenylene, or 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position;

wherein L is a group of the formula -CO.NH-; and

Y is a group of the formula -A-Y¹ in which A is methylene and Y¹ is 2-nitrophenyl, 3-nitrophenyl, 3-cyanophenyl, 4-carboxyphenyl or 3-trifluoromethylphenyl, or Y¹ is 5-thiazolyl, 2,3-dihydro-4-oxoquinazolin-6-yl, 2,3-dihydro-2-methyl-4-oxoquinazolin-6-yl or 2,3-dihydro-2,3-dimethyl-4-oxoquinazolin-

6-yl;

or a pharmaceutically-acceptable salt thereof.

6. A process as claimed in claim 1 for the manufacture of a quinazoline selected from the group of compounds:-
- p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)benzamide;
- p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-trifluoromethylbenzyl)benzamide;
- p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)benzamide;
- p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-o-fluoro-N-(3-nitrobenzyl)benzamide;
- 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide;
- p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;
- p-[N-(2-amino-3,4-dihydro-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;
- p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)benzamide and
- p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide;
- or a pharmaceutically-acceptable salt thereof.
7. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is alkyl or alkoxy each of up to 6 carbon atoms;
- or R¹ is alkyl of up to 3 carbon atoms which bears a hydroxy substituent, or which bears one, two or three fluoro substituents;
- or R¹ is hydroxyalkoxy of up to 3 carbon atoms or alkoxyalkoxy of up to 6 carbon atoms;
- wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from halogeno and from alkyl and alkoxy each of up to 3 carbon atoms;
- wherein R² is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, halogenoalkyl or cyanoalkyl each of up to 6 carbon atoms;
- wherein Ar is phenylene or heterocyclene which may be unsubstituted or may bear one or two substituents selected from halogeno, hydroxy and amino, and from alkyl, alkoxy and halogenoalkyl each of up to 3 carbon atoms;
- wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- or -CO.O-, wherein R³ is alkyl of up to 6 carbon atoms;
- and
- wherein Y is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof; or Y is a group of the formula -A-Y¹ in which A is alkylene, cycloalkylene, alkenylene or alkynylene each of up to 6 carbon atoms, and Y¹ is aryl of up to 10 carbon atoms, or heteroaryl or a hydrogenated derivative thereof;
- wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl, sulphonyl or imino group or an alkylimino group of up to 6 carbon atoms;
- and wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsubstituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy and halogeno, from alkyl, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxycarbonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, alkoxy, halogenoalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, carbamoylalkyl, N-alkylcarbamoylalkyl and N,N-dialkylcarbamoylalkyl each of up to 6 carbon atoms and from phenyl and phenylalkyl of up to 10 carbon atoms, and wherein each of said phenyl groups may bear a substituent selected from halogeno and from alkyl and alkoxy each of up to 3 carbon atoms;
- or a pharmaceutically-acceptable salt thereof;
- provided that when R¹ is all of up to 6 carbon atoms, the quinazoline ring bears no further substituents or bears one further substituent selected from halogeno and alkyl of up to 3 carbon atoms, R² is alkyl, alkenyl or alkynyl each of up to 6 carbon atoms,

Ar is phenylene which is unsubstituted or bears one or two substituents selected from halogeno, hydroxy and amino, and

L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.

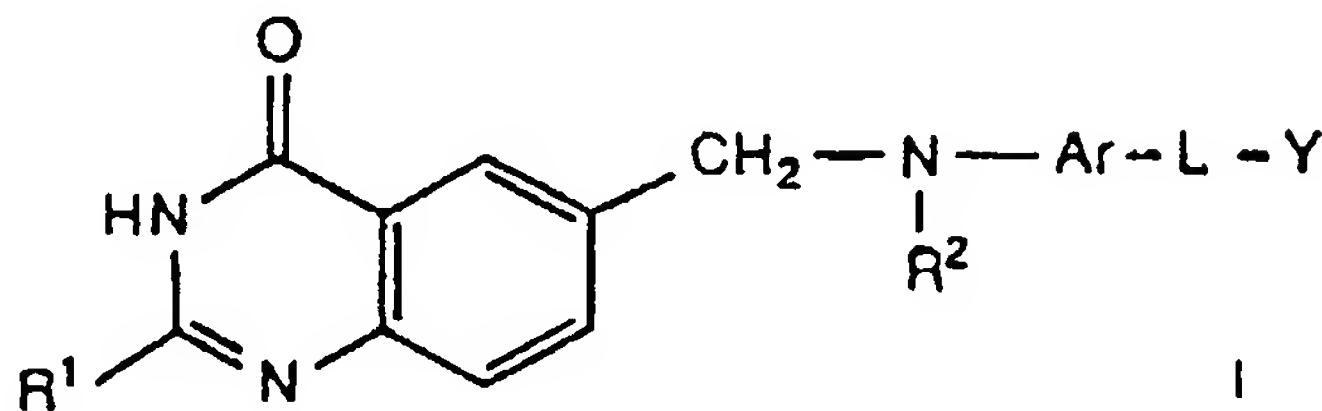
- 5 8. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is methyl, ethyl, methoxy or fluoromethyl;
 wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;
 wherein R² is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;
 10 wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene, thiazolylene or thiadiazolylene which is unsubstituted or which bears one or two substituents selected from fluoro, chloro, bromo, hydroxy, amino, methyl, methoxy and trifluoromethyl;
 wherein L is a group of the formula -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-,
 15 -CO.CH₂- or -CO.O-, wherein R³ is methyl or ethyl; and
 Y is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4- triazolyl, thiadiazolyl or tetrazolyl; or
 Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene, trimethylene, propylidene, propylene, 1-isopropylethylene or tetramethylene and Y¹ is phenyl, naphthyl, pyridyl,
 20 quinolyl, isoquinolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4- triazolyl, thiadiazolyl or tetrazolyl;
 wherein one constituent methylene group in A may be replaced by an oxy, thio, sulphinyl or sulphonyl group; and
 wherein each of said aryl or heteroaryl groups, or hydrogenated derivatives thereof, may be unsub-
 25 stituted or may bear one or two substituents selected from hydroxy, amino, nitro, cyano, carbamoyl, carboxy, fluoro, chloro, bromo, methyl, ethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, isopropylsulphinyl, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, methoxy, ethoxy,
 30 trifluoromethyl, carboxymethyl, 2-carboxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, phenyl, benzyl, phenethyl or phenylpropyl, and wherein each of said phenyl groups may bear a substituent selected from fluoro, chloro, bromo, methyl, ethyl, methoxy and ethoxy;
 or a pharmaceutically acceptable salt thereof;
 provided that when R¹ is methyl or ethyl, the quinazoline ring bears no further substituents or bears one
 35 further substituent selected from fluoro, chloro and methyl,
 R² is methyl, ethyl, propyl, prop-2-enyl or prop-2-ynyl,
 Ar is 1,4-phenylene which is unsubstituted or bears one or two substituents selected from fluoro, chloro, bromo, hydroxy and amino, and
 L is a group of the formula -CONH-, then Y is not tetrazol-5-yl.
- 40 9. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is methyl, ethyl, methoxy or fluoromethyl;
 wherein the quinazoline ring may bear no further substituents or may bear one further substituent selected from fluoro, chloro, methyl and methoxy;
 45 wherein R² is hydrogen, methyl, ethyl, propyl, prop-2-enyl, prop-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl, 2-bromoethyl or cyanomethyl;
 wherein Ar is 1,4-phenylene, thien-2,5-diyl, pyrid-2,5-diyl or thiazol-2,5-diyl which is unsubstituted or which bears one or two substituents selected from fluoro, chloro, hydroxy, amino and methyl;
 wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and
 50 Y is phenyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl or 1,2,3-triazolyl; or
 Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene or trimethylene and Y¹ is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, pyrimidinyl, indolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiadiazolyl or tetrazolyl; and
 wherein each of said aryl or heteroaryl groups may be unsubstituted or may bear one or two
 55 substituents selected from amino, nitro, fluoro, methyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, methylsulphinyl, methylsulphonyl, methoxy, trifluoromethyl or benzyl;
 or a pharmaceutically-acceptable salt thereof.

10. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is methyl; wherein R² is hydrogen, methyl, ethyl, prop-2-ynyl or 2-fluoroethyl; wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl or thiazol-2,5-diyl each with the group -L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position; wherein L is a group of the formula -CO.NH-, -CO.NR³- or -CO.O-, wherein R³ is methyl or ethyl; and wherein Y is phenyl; or Y is a group of the formula -A-Y¹ in which A is methylene, ethylene, ethylidene or trimethylene and Y¹ is phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-indolyl, 3-indolyl, 1-imidazolyl, 2-imidazolyl, 2-benzimidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 3-indazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl, 1,2,4-triazol-1-yl, 2-thiadiazolyl or 5-tetrazolyl; and wherein each of said aryl or heteroaryl groups may be unsubstituted or may bear one or two substituents selected from amino, nitro, carbamoyl, fluoro, methyl, ethoxycarbonyl, methylsulphinyl, methylsulphonyl, methoxy, trifluoromethyl or benzyl; or a pharmaceutically-acceptable salt thereof.
11. A process as claimed in claim 1 for the manufacture of a quinazoline of the formula I wherein R¹ is methyl; wherein R² is methyl, ethyl or prop-2-ynyl; wherein Ar is 1,4-phenylene or thien-2,5-diyl, or is pyrid-2,5-diyl or thiazol-2,5-diyl each with the group -L-Y in the 2-position, or is 2-fluoro-1,4-phenylene with the group -L-Y in the 1-position; wherein L is a group of the formula -CO.NH- and Y is a group of the formula -A-Y¹ in which A is methylene or ethylene and Y¹ is 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-indolyl or 1,2,4-triazol-1-yl, or Y¹ is phenyl which may be unsubstituted or may bear a substituent selected from amino, nitro, ethoxycarbonyl or trifluoromethyl; or a pharmaceutically-acceptable salt thereof.
12. A process as claimed in claim 1 for the manufacture of a quinazoline selected from the group of compounds:-
N-benzyl-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)-benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylmethyl)-benzamide;
p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)-benzamide and
N-benzylimidazol-2-ylmethyl p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-ethylamino]-benzoate.
13. A process for the manufacture of a pharmaceutical composition characterised by bringing into admixture a quinazoline as defined in any one of claims 1 to 12, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.
14. The use of a quinazoline as defined in any one of claims 1 to 12, or a pharmaceutically-acceptable salt thereof, in the manufacture of a novel medicament for use in the production of an anti-tumour effect in a warm blooded animal such as man.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Chinazolin mit der folgenden Formel I:



in der

R¹ für Wasserstoff oder Amino oder für Alkyl oder Alkoxy steht, die jeweils bis zu 6 Kohlenstoffatome enthalten;

oder in der R¹ für Alkyl mit bis zu 3 Kohlenstoffatomen steht, das einen Hydroxy-Substituenten trägt, oder das einen, zwei oder drei Fluor-Substituenten trägt;

oder in der R¹ für Hydroxyalkoxy mit bis zu 3 Kohlenstoffatomen oder für Alkoxyalkoxy mit bis zu 6 Kohlenstoffatomen steht;

wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen kann, der aus Halogen und aus Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;

R² für Wasserstoff, Alkyl, Alkenyl, Alkynyl, Hydroxyalkyl, Halogenalkyl oder Cyanoalkyl mit jeweils bis zu 6 Kohlenstoffatomen steht;

Ar für Phenylen oder Heterocyclen steht, das unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus Halogen, Hydroxy, Amino und Nitro und aus Alkyl, Alkoxy und Halogenalkyl mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt sind;

L für eine Gruppe mit der Formel -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- oder -CO.O- steht, wobei R³ für Alkyl mit bis zu 6 Kohlenstoffatomen steht; und

Y für Aryl mit bis zu 10 Kohlenstoffatomen oder für Heteroaryl oder für ein hydriertes Derivat davon steht; oder in der

Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Alkylen, Cycloalkylen, Alkenylen oder Alkinylen mit jeweils bis zu 6 Kohlenstoffatomen steht, und in der Y¹ für Aryl mit bis zu 10 Kohlenstoffatomen oder für Heteroaryl oder ein hydriertes Derivat davon steht;

wobei ein Methylen-Gruppen-Bestandteil in A durch eine Oxy-, Thio, Sulfinyl-, Sulfonyl- oder Imino-Gruppe oder eine Alkylimino-Gruppe mit bis zu 6 Kohlenstoffatomen ersetzt sein kann,

und wobei jede der Aryl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein können oder bis zu drei Substituenten tragen können, die aus folgendem ausgewählt sind:

Hydroxy, Oxo, Amino, Nitro, Cyano, Carbamoyl, Sulfamoyl, Carboxy und Halogen, Alkyl, Alkylamino, Dialkylamino, N-Alkylcarbamoyl, N,N-Dialkylcarbamoyl, Alkoxy, Alkanoyloxyalkyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Alkoxy, Halogenalkyl, Hydroxyalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Alkoxyalkyl, Carbamoylalkyl, N-Alkylcarbamoylalkyl und N,N-Dialkylcarbamoylalkyl mit jeweils bis zu 6 Kohlenstoffatomen und Phenyl, Pyridyl und Phenylalkyl mit bis zu 10 Kohlenstoffatomen, wobei jede der Phenyl- oder Phenylalkyl-Gruppen einen Substituenten tragen kann, der aus Halogen und Nitro und Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;

oder ein pharmazeutisch geeignetes Salz davon;

mit der Maßgabe, daß, wenn R¹ für Wasserstoff oder Amino oder für Alkyl mit bis zu 6 Kohlenstoffatomen steht und L für eine Gruppe mit der Formel -CONH- steht, Y dann nicht für Tetrazolyl steht.

2. Chinazolin mit der Formel I nach Anspruch 1,

wobei R¹ für Wasserstoff oder Amino oder für Methyl, Ethyl, Methoxy oder Fluormethyl steht;

wobei der Chinazolin-Ring keine weitere Substituenten tragen kann, oder einen weiteren Substituenten tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;

wobei R² für Methyl, Ethyl, Propyl, Prop-2-enyl, Prop-2-ynyl, 2-Hydroxyethyl, 3-Hydroxypropyl, 2-

- Fluorethyl, 2-Bromethyl oder Cyanomethyl steht;
 wobei Ar für 1,4-Phenylen, Thienylen, Pyridylen, Pyrimidinylen oder Thiazolylen steht, das unsubstituiert ist, oder einen Substituenten trägt, der aus Fluor, Chlor, Brom, Hydroxy, Amino, Nitro, Methyl, Methoxy oder Trifluormethyl ausgewählt ist;
 5 wobei L für eine Gruppe mit der Formel $-CO.NH-$, $-CO.NR^3-$ oder $-CO.O-$ steht, wobei R^3 für Methyl oder Ethyl steht; und
 wobei Y für Phenyl, 2,5-Dioxopyrrolidinyl oder 2,6-Dioxopiperidinyl steht, oder wobei Y für eine Gruppe mit der Formel $-A-Y^1$ steht, in der A für Methylen, Ethylen, Ethylidin, Trimethylen, Propyliden, Propylen, Butyliden, Isobutyliden oder Tetramethylen steht, und Y^1 für Phenyl, Furyl, Thienyl, Pyridyl, Chinolyl, Isochinolyl, Pyrazinyl, Pyrimidinyl, Chinazolinyl, Pyridazinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Oxazolyl, Isoxazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Tetrazolyl oder Hexahydro-2-oxoazepin-1-yl steht;
 10 wobei ein Methylen-Gruppen-Bestandteil in A durch eine Thio-, Sulfinyl-, Sulfonyl- oder Imino-Gruppe ersetzt sein kann; und
 15 wobei jede der Phenyl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein kann oder bis zu drei Substituenten tragen kann, die aus folgendem ausgewählt sind: Hydroxy, Oxo, Amino, Nitro, Cyano, Carbamoyl, Sulfamoyl, Carboxy, Fluor, Chlor, Brom, Methyl, Ethyl, Methylamino, Ethylamino, Dimethylamino, Diethylamino, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Methoxycarbonyl, Ethoxycarbonyl, tert-Butoxycarbonyl, Isobutyryloxymethyl, Pivaloyloxymethyl, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Methoxy, Ethoxy, Trifluormethyl, Carboxymethyl, 1-Carboxyethyl, 2-Carboxyethyl, 3-Carboxypropyl, Carbamoylmethyl, N-Methylcarbamoylmethyl, N,N-Dimethylcarbamoylmethyl, Phenyl, Pyridyl, Benzyl, Phenethyl oder Phenylpropyl, und wobei jede Phenyl-Gruppe in den Substituenten einen Substituenten tragen kann, der aus Fluor, Chlor, Brom, Nitro, Methyl, Ethyl, Methoxy und Ethoxy ausgewählt ist,
 20 oder ein pharmazeutisch geeignetes Salz davon.
 25
3. Chinazolin mit der Formel I nach Anspruch 1,
 wobei R^1 für Amino, Methyl, Methoxy oder Fluormethyl steht;
 wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten
 30 tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;
 wobei R^2 für Methyl, Ethyl, Prop-2-enyl oder Prop-2-inyl steht;
 wobei Ar für 1,4-Phenylen, Thienylen, Pyridylen oder Thiazolylen steht, das unsubstituiert ist, oder das einen Fluor- oder Nitro-Substituenten trägt;
 wobei L für eine Gruppe mit der Formel $-CO.NH-$ oder $-CO.O-$ steht; und wobei Y für Phenyl steht, oder
 35 wobei Y für eine Gruppe mit der Formel $-A-Y^1$ steht, in der A für Methylen, Ethylen, Ethyliden, Trimethylen, Propyliden, Propylen oder Isobutyliden steht und Y^1 für Phenyl, 2-Thienyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 3-Chinolyl, 4-Chinolyl, 8-Chinolyl, 2-Pyrimidinyl, 4-Pyrimidinyl, 6-Chinazolinyl, 3-Indolyl, 1-Imidazolyl, 2-Imidazolyl, 4-Imidazolyl, 2-Benzimidazolyl, 2-Thiazolyl, 5-Thiazolyl, 1,2,4-Triazol-1-yl, 1,2,4-Triazol-3-yl oder Tetrazol-5-yl steht, oder wobei Y für Phenylsulfonyl steht; und wobei jede
 40 der Phenyl- oder Heteroaryl-Gruppen unsubstituiert sein kann oder bis zu drei Substituenten tragen kann, die aus folgendem ausgewählt sind: Hydroxy, Oxo, Amino, Nitro, Cyano, Carbamoyl, Carboxy, Fluor, Chlor, Methyl, Ethyl, N-Methylcarbamoyl, N,N-Dimethylcarbamoyl, Methoxycarbonyl, Ethoxycarbonyl, Pivaloyloxymethyl, Methoxy, Trifluormethyl, Carboxymethyl, 1-Carboxyethyl, 2-Carboxyethyl, 3-Carboxypropyl, 4-Pyridyl und Benzyl;
 45 oder ein pharmazeutisch geeignetes Salz davon.
4. Chinazolin mit der Formel I nach Anspruch 1,
 wobei R^1 für Amino, Methyl oder Methoxy steht;
 wobei der Chinazolin-Ring einen Methyl-Substituenten in der 7-Stellung tragen kann;
 50 wobei R^2 für Methyl, Ethyl oder Prop-2-inyl steht;
 wobei Ar für 1,4-Phenylen oder Thien-2,5-diyl steht oder für Pyrid-2,5-diyl mit der Gruppe $-L-Y$ in der 2-Stellung oder für 2-Fluor-1,4-phenylen mit der Gruppe $-L-Y$ in der 1-Stellung steht;
 wobei L für eine Gruppe mit der Formel $-CONH-$ steht; und
 wobei Y für Benzyl oder Phenylsulfonyl steht, das einen Nitro-, Cyano-, Carboxy- oder Trifluormethyl-Substituenten tragen kann, oder wobei Y für Thiazol-5-ylmethyl oder 1,2,3,6-Tetrahydro-2,6-dioxypyrimidin-4-ylmethyl steht, oder wobei Y für 2,3-Dihydro-4-oxochinazolin-6-ylmethyl steht, das einen oder
 55 zwei Methyl-Substituenten tragen kann;
 oder ein pharmazeutisch geeignetes Salz davon.

5. Chinazolin mit der Formel I nach Anspruch 1,
wobei R¹ für Methyl steht;
wobei der Chinazolin-Ring einen Methyl-Substituenten in der 7-Stellung tragen kann;
wobei R² für Methyl oder Prop-2-ynyl steht;
5 wobei Ar für 1,4-Phenylen steht oder für 2-Fluor-1,4-phenylen mit der Gruppe -L-Y in der 1-Stellung;
wobei L für eine Gruppe mit der Formel -CO.NH- steht; und
wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen steht und Y¹ für 2-Nitrophenyl, 3-Nitrophenyl, 3-Cyanophenyl, 4-Carboxyphenyl oder 3-Trifluormethylphenyl steht, oder in
10 der Y¹ für 5-Thiazolyl, 2,3-Dihydro-4-oxochinazolin-6-yl, 2,3-Dihydro-2-methyl-4-oxochinazolin-6-yl oder
2,3-Dihydro-2,3-dimethyl-4-oxochinazolin-6-yl steht;
oder ein pharmazeutisch geeignetes Salz davon.
6. Chinolin mit der Formel I nach Anspruch 1, das aus der folgenden Gruppe von Verbindungen
ausgewählt ist:-
15 p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-
methyl-4-oxochinazolin-6-ylmethyl)benzamid;
p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-
trifluormethylbenzyl)benzamid;
p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)-
20 benzamid;
p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-methylamino]-o-fluor-N-(3-nitrobenzyl)-
benzamid;
5-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-
pyridin-2-carboxamid;
25 p-[N-(3,4-Dihydro-2-methoxy-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-
benzamid;
p-[N-(2-Amino-3,4-dihydro-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-
benzamid;
p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)-
30 benzamid und
p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-
benzamid;
oder ein pharmazeutisch geeignetes Salz davon.
- 35 7. Chinazolin mit der Formel I nach Anspruch 1,
wobei R¹ für Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen steht;
oder wobei R¹ für Alkyl mit bis zu 3 Kohlenstoffatomen steht, das einen Hydroxy-Substituenten trägt,
oder das einen, zwei oder drei Fluor-Substituenten trägt;
40 oder wobei R¹ für Hydroxyalkoxy mit bis zu 3 Kohlenstoffatomen steht oder für Alkoxyalkoxy mit bis zu
6 Kohlenstoffatomen;
wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten
tragen kann, der aus Halogen und aus Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen
ausgewählt ist;
wobei R² für Wasserstoff, Alkyl, Alkenyl, Alkynyl, Hydroxyalkyl, Halogenalkyl oder Cyanoalkyl mit jeweils
45 bis zu 6 Kohlenstoffatomen steht;
wobei Ar für Phenylen oder Heterocyclen steht, das unsubstituiert sein kann oder einen oder zwei
Substituenten tragen kann, die aus Halogen, Hydroxy und Amino und aus Alkyl, Alkoxy und Halogenal-
kyl mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt sind;
wobei L für eine Gruppe mit der Formel -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂-O-,
50 -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- oder -CO.O- steht, wobei R³ für Alkyl mit bis zu 6
Kohlenstoffatomen steht; und
wobei Y für Aryl mit bis zu 10 Kohlenstoffatomen steht, oder für Heteroaryl oder ein hydriertes Derivat
davon; oder
wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Alkylen, Cycloalkylen, Alkenylen oder
55 Alkinylen mit jeweils bis zu 6 Kohlenstoffatomen steht, und Y¹ für Aryl mit bis zu 10 Kohlenstoffatomen,
oder für Heteroaryl oder ein hydriertes Derivat davon steht;
wobei ein Methylen-Gruppen-Bestandteil in A durch eine Oxy-, Thio-, Sulfinyl-, Sulfonyl- oder Imino-
Gruppe oder eine Alkylimino-Gruppe mit bis zu 6 Kohlenstoffatomen ersetzt sein kann; und

wobei jede der Aryl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein können oder einen oder zwei Substituenten tragen können, die aus folgendem ausgewählt sind: Hydroxy, Amino, Nitro, Cyano, Carbamoyl, Carboxy und Halogen, Alkyl, Alkylamino, Dialkylamino, N-Alkylcarbamoyl, N,N-Dialkylcarbamoyl, Alkoxycarbonyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Alkoxy, Halogenalkyl, Hydroxyalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Alkoxycarbonylalkyl, Carbamoylalkyl, N-Alkylcarbamoylalkyl und N,N-Dialkylcarbamoylalkyl mit jeweils bis zu 6 Kohlenstoffatomen und Phenyl und Phenylalkyl mit bis zu 10 Kohlenstoffatomen, wobei jede der Phenyl-Gruppen einen Substituenten tragen kann, der aus Halogen und aus Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;

oder ein pharmazeutisch geeignetes Salz davon;

mit der Maßgabe, daß, wenn R¹ für Alkyl mit bis zu 6 Kohlenstoffatomen steht, der Chinazolin-Ring keine weiteren Substituenten trägt oder einen weiteren Substituenten trägt, der aus Halogen und Alkyl mit bis zu 3 Kohlenstoffatomen ausgewählt ist, R² für Alkyl, Alkenyl oder Alkinyl mit jeweils bis zu 6 Kohlenstoffatomen steht, Ar für Phenylen steht, das unsubstituiert ist oder einen oder zwei Substituenten trägt, die aus Halogen, Hydroxy und Amino ausgewählt sind, und L für eine Gruppe mit der Formel -CONH- steht, Y dann nicht für Tetrazol-5-yl steht.

8. Chinazolin mit der Formel 1 nach Anspruch 1,
- wobei R¹ für Methyl, Ethyl, Methoxy oder Fluormethyl steht;
- wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;
- wobei R² für Wasserstoff, Methyl, Ethyl, Propyl, Prop-2-enyl, Prop-2-inyl, 2-Hydroxyethyl, 3-Hydroxypropyl, 2-Fluorethyl, 2-Bromomethyl oder Cyanomethyl steht;
- wobei Ar für 1,4-Phenylen, Thienylen, Pyridylen, Pyrimidinylen, Thiazolylen oder Thiadiazolylen steht;
- das unsubstituiert ist oder einen oder zwei Substituenten trägt, die aus Fluor, Chlor, Brom, Hydroxy, Amino, Methyl, Methoxy und Trifluormethyl ausgewählt sind;
- wobei L für eine Gruppe mit der Formel -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -CO.CH₂- oder -CO.O- steht, wobei R³ für Methyl oder Ethyl steht; und
- wobei Y für Phenyl, Naphthyl, Pyridyl, Chinolyl, Isochinolyl, Pyrimidinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Oxazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Thiadiazolyl oder Tetrazolyl steht; oder
- wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen, Ethylen, Ethyliden, Trimethylen, Propyliden, Propylen, 1-Isopropylethylen oder Tetramethylen steht und Y¹ für Phenyl, Naphthyl, Pyridyl, Chinolyl, Isochinolyl, Pyrazinyl, Pyrimidinyl, Pyridazinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Oxazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Thiadiazolyl oder Tetrazolyl steht;
- wobei ein Methylen-Gruppen-Bestandteil in A durch eine Oxy-, Thio-, Sulfinyl- oder Sulfonyl-Gruppe ersetzt sein kann; und
- wobei jede der Aryl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus folgendem ausgewählt sind: Hydroxy, Amino, Nitro, Cyano, Carbamoyl, Carboxy, Fluor, Chlor, Brom, Methyl, Ethyl, Methylamino, Ethylamino, Dimethylamino, Diethylamino, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Methoxy-carbonyl, Ethoxycarbonyl, tert-Butoxycarbonyl, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Isopropylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Isopropylsulfonyl, Methoxy, Ethoxy, Trifluormethyl, Carboxymethyl, 2-Carboxyethyl, Carbamoylmethyl, N-Methylcarbamoylmethyl, N,N-Dimethylcarbamoylmethyl, Phenyl, Benzyl, Phenethyl oder Phenylpropyl, und wobei jede der Phenyl-Gruppen einen Substituenten tragen kann, der aus Fluor, Chlor, Brom, Methyl, Ethyl, Methoxy und Ethoxy ausgewählt ist;
- oder ein pharmazeutisch geeignetes Salz davon;
- mit der Maßgabe, daß, wenn R¹ für Methyl oder Ethyl steht, der Chinazolin-Ring keine weiteren Substituenten trägt oder einen weiteren Substituenten trägt, der aus Fluor, Chlor und Methyl ausgewählt ist,
- R² für Methyl, Ethyl, Propyl, Prop-2-enyl oder Prop-2-inyl steht, Ar für 1,4-Phenylen steht, das unsubstituiert ist oder einen oder zwei Substituenten trägt, die aus Fluor, Chlor, Brom, Hydroxy und Amino ausgewählt sind, und
- L für eine Gruppe mit der Formel -CONH- steht, Y dann nicht für Tetrazol-5-yl steht.

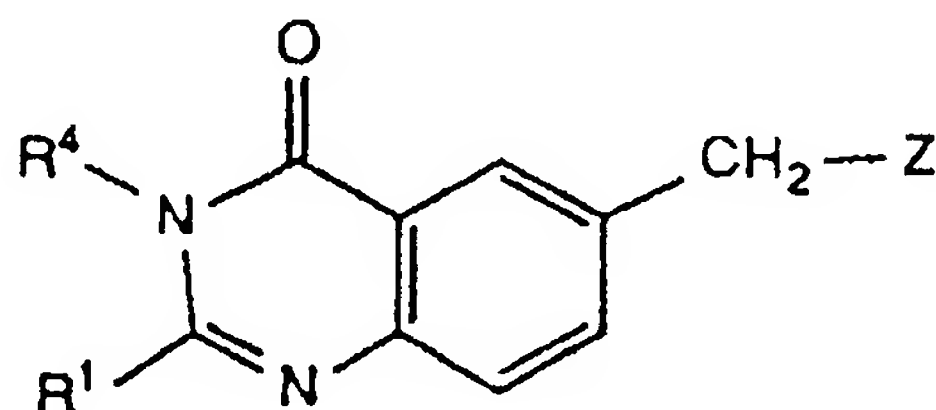
9. Chinazolin mit der Formel I nach Anspruch 1,
wobei R¹ für Methyl, Ethyl, Methoxy oder Fluormethyl steht;
wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten
tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;
5 wobei R² für Wasserstoff, Methyl, Ethyl, Propyl, Prop-2-enyl, Prop-2-ynyl, 2-Hydroxyethyl, 3-Hydrox-
ypropyl, 2-Fluorethyl, 2-Bromomethyl oder Cyanomethyl steht;
wobei Ar für 1,4-Phenylen, Thien-2,5-diyl, Pyrid-2,5-diyl oder Thiazol-2,5-diyl steht, das unsubstituiert
ist oder das einen oder zwei Substituenten trägt, die aus Fluor, Chlor, Hydroxy, Amino und Methyl
ausgewählt sind;
10 wobei L für eine Gruppe mit der Formel -CO.NH-, -CO.NR³- oder -CO.O- steht, wobei R³ für Methyl
oder Ethyl steht; und
wobei Y für Phenyl, Pyridyl, Pyrimidinyl, Imidazolyl, Thiazolyl oder 1,2,3-Triazolyl steht; oder
wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen, Ethylen, Ethyliden oder
Trimethylen steht und Y¹ für Phenyl, Naphthyl, Pyridyl, Chinolyl, Isochinolyl, Pyrimidinyl, Indolyl,
15 Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Thiadiazolyl
oder Tetrazolyl steht; und
wobei jede der Aryl- oder Heteroaryl-Gruppen unsubstituiert sein kann oder einen oder zwei Substituen-
ten tragen kann, die aus Amino, Nitro, Fluor, Methyl, Carbamoyl, N-Methylcarbamoyl, N,N-Dimethylcar-
bamoyl, Methoxycarbonyl, Ethoxycarbonyl, Methylsulfinyl, Methylsulfonyl, Methoxy, Trifluormethyl oder
20 Benzyl ausgewählt sind;
oder ein pharmazeutisch geeignetes Salz davon.
10. Chinazolin mit der Formel I nach Anspruch 1,
wobei R¹ für Methyl steht; wobei R² für Wasserstoff, Methyl, Ethyl, Prop-2-ynyl oder 2-Fluorethyl steht;
25 wobei Ar für 1,4-Phenylen oder Thien-2,5-diyl oder für Pyrid-2,5-diyl oder für Thiazol-2,5-diyl mit der
Gruppe -L-Y jeweils in der 2-Stellung oder für 2-Fluor-1,4-Phenylen mit der Gruppe -L-Y in der 1-
Stellung steht;
wobei L für eine Gruppe mit der Formel -CO.NH-, -CO.NR³- oder -CO.O- steht, wobei R³ für Methyl
oder Ethyl steht; und
30 worin Y für Phenyl steht; oder
wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen, Ethylen, Ethyliden oder
Trimethylen steht und Y¹ für Phenyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 1-Isochinolyl, 3-Isochinolyl, 4-
Isochinolyl, 2-Pyrimidinyl, 4-Pyrimidinyl, 5-Pyrimidinyl, 2-Indolyl, 3-Indolyl, 1-Imidazolyl, 2-Imidazolyl, 2-
Benzimidazolyl, 1-Pyrazolyl, 3-Pyrazolyl, 4-Pyrazolyl, 3-Indazolyl, 2-Thiazolyl, 4-Thiazolyl, 5-Thiazolyl,
35 1,2,3-Triazol-4-yl, 1,2,4-Triazol-3-yl, 1,2,4-Triazol-4-yl, 1,2,4-Triazol-1-yl, 2-Thiadiazolyl oder 5-Tetrazolyl
steht; und
wobei jede der Aryl- oder Heteroaryl-Gruppen unsubstituiert sein kann oder einen oder zwei Substituen-
ten tragen kann, die aus Amino, Nitro, Carbamoyl, Fluor, Methyl, Ethoxycarbonyl, Methylsulfinyl,
Methylsulfonyl, Methoxy, Trifluormethyl oder Benzyl ausgewählt sind;
40 oder ein pharmazeutisch geeignetes Salz davon.
11. Chinazolin mit der Formel I nach Anspruch 1,
wobei R¹ für Methyl steht; wobei R² für Methyl, Ethyl oder Prop-2-ynyl steht;
wobei Ar für 1,4-Phenylen oder Thien-2,5-diyl steht, oder für Pyrid-2,5-diyl oder Thiazol-2,5-diyl mit der
45 Gruppe -L-Y jeweils in der 2-Stellung oder für 2-Fluor-1,4-phenylen mit der Gruppe -L-Y in der 1-
Stellung;
wobei L für eine Gruppe mit der Formel -CO.NH- steht, und
wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen oder Ethylen steht und Y¹
für 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 3-Indolyl oder 1,2,4-Triazol-1-yl steht, oder in der Y¹ für Phenyl steht,
50 das unsubstituiert sein kann oder einen Substituenten tragen kann, der aus Amino, Nitro, Ethoxycarbo-
nyl oder Trifluormethyl ausgewählt ist;
oder ein pharmazeutisch geeignetes Salz davon.
12. Chinazolin mit der Formel I nach Anspruch 1, das aus der folgenden Gruppe von Verbindungen
ausgewählt ist:-
55 N-Benzyl-p-[N-(3,4-dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamid,
p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)-
benzamid;

p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylmethyl)-benzamid;

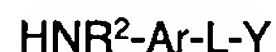
p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)-benzamid und

N-Benzylimidazol-2-ylmethyl-p-[N-(3,4-dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-ethylamino]-benzoat.

13. Verfahren zur Herstellung eines Chinazolins nach einem der Ansprüche 1 bis 12, bei dem:-
(a) eine Verbindung mit der folgenden Formel II

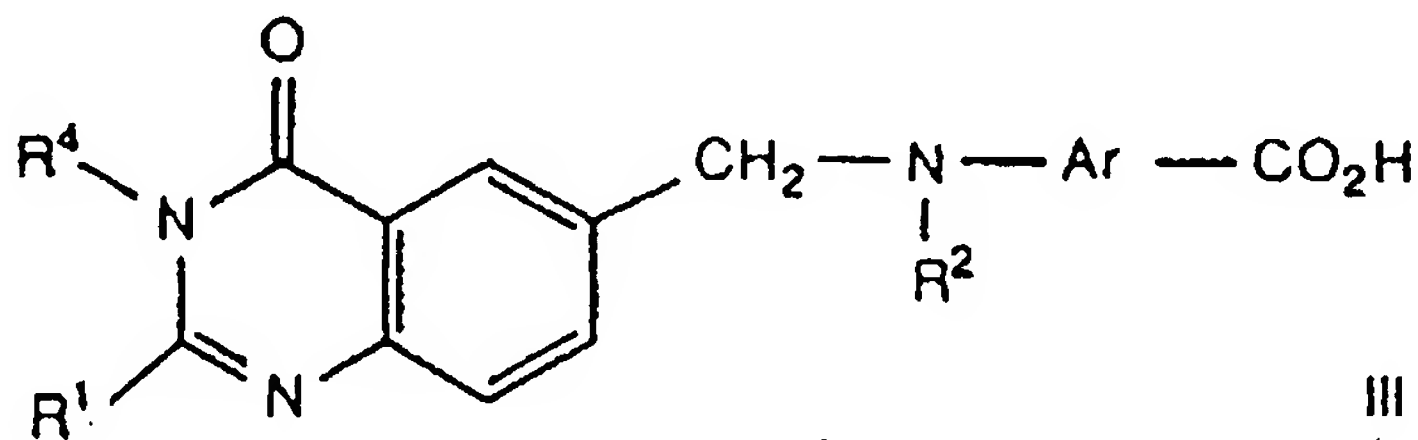


in der R¹ die in Anspruch 1 angegebene Bedeutung hat, mit der Maßgabe, daß, wenn R¹ für Amino, Hydroxyalkyl oder Hydroxyalkoxy steht, jede Amino- oder Hydroxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt ist, R⁴ für Wasserstoff oder eine Schutzgruppe steht und Z für eine austauschbare Gruppe steht, mit einer Verbindung mit der folgenden Formel:-



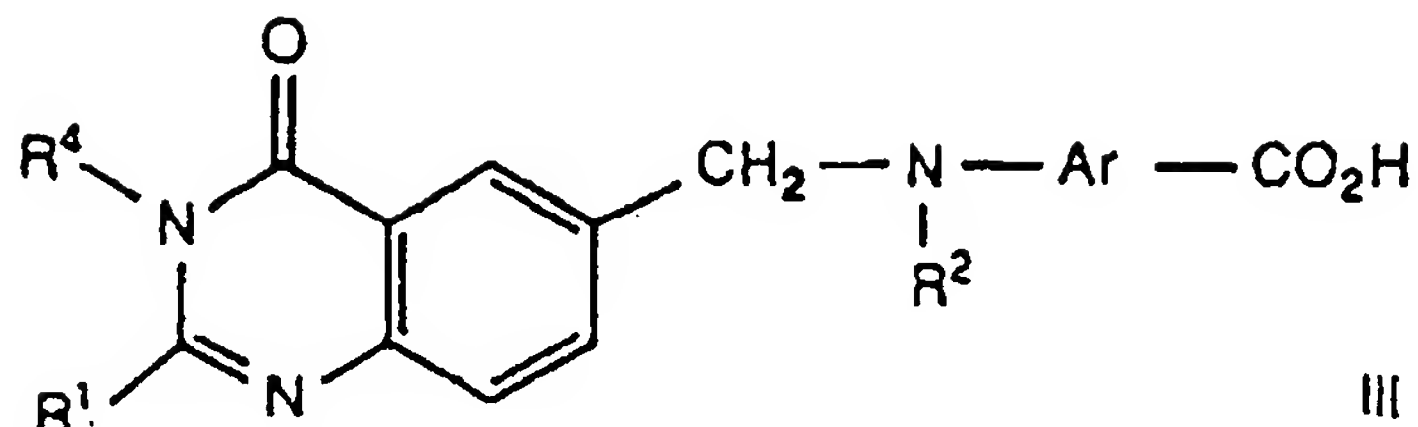
in der R², Ar, L und Y die in Anspruch 1 angegebenen Bedeutungen haben, umgesetzt wird, mit der Maßgabe, daß, wenn eine Amino-, Alkylamino-, Imino-, Hydroxy- oder Carboxy-Gruppe in R², Ar oder Y vorhanden ist, jede Amino-, Alkylamino-, Imino- und Carboxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt ist und jede Hydroxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt sein kann oder alternativ keine Hydroxy-Gruppe geschützt werden muß; wonach jede unerwünschte Schutzgruppe in R¹, R², Ar und Y entfernt wird;

(b) zur Herstellung eines Chinazolins nach Anspruch 1, bei dem L für eine Gruppe mit der Formel -CONH- oder -CONR³- steht, eine Säure mit der folgenden Formel III, oder ein reaktives Derivat davon



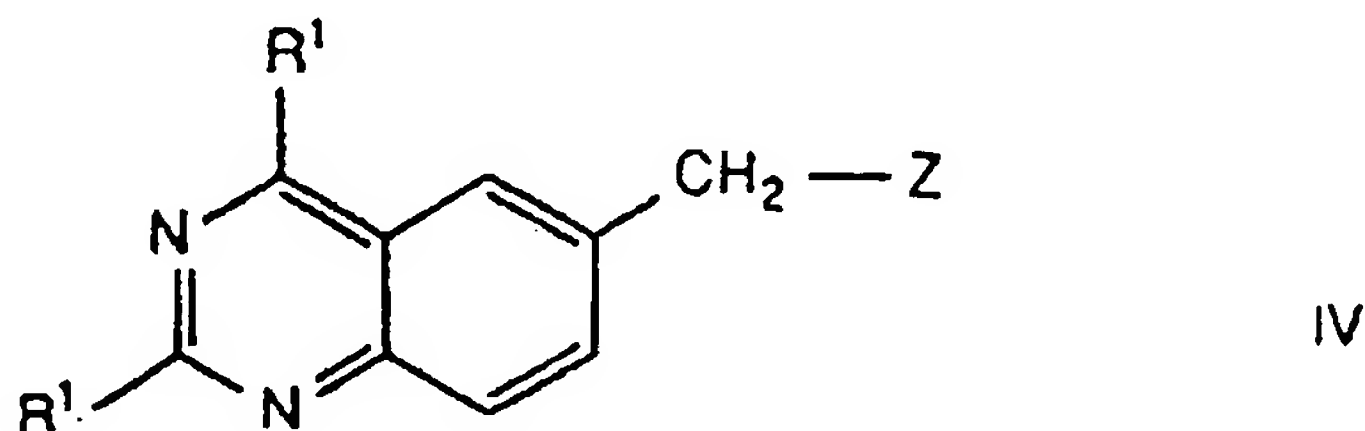
mit einer Verbindung mit der Formel H₂N-Y oder R³NH-Y umgesetzt wird, wobei R¹, R², R³, R⁴, Ar und Y die in Anspruch 1 angegebenen Bedeutungen haben und jede Amino-, Alkylamino-, Imino- und Carboxy-Gruppe in R¹; Ar und Y mit einer herkömmlichen Schutzgruppe geschützt ist und jede Hydroxy-Gruppe in R¹, R², Ar und Y mit einer herkömmlichen Schutzgruppe geschützt sein kann oder alternativ keine Hydroxy-Gruppe geschützt werden muß; wonach die Schutzgruppen mit herkömmlichen Mitteln entfernt werden;

(c) zur Herstellung eines Chinazolins nach Anspruch 1, bei dem L für eine Gruppe mit der Formel -CO.O- steht, eine Säure mit der folgenden Formel III, oder ein reaktives Derivat davon, in Gegenwart einer geeigneten Base

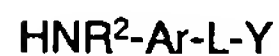


mit einer Verbindung mit der Formel HO-Y umgesetzt wird, wobei R¹, R², R³, R⁴, Ar und Y die in Anspruch 1 angegebenen Bedeutungen haben und jede Amino-, Alkylamino-, Imino-, Hydroxy- und Carboxy-Gruppe in R¹, R², Ar und Y mit einer herkömmlichen Schutzgruppe geschützt ist; wonach die Schutzgruppen mit herkömmlichen Mitteln entfernt werden;

(d) zur Herstellung eines Chinazolins nach Anspruch 1, bei dem R¹ für Alkoxy, Hydroxyalkoxy oder Alkoxyalkoxy steht, eine Verbindung mit der folgenden Formel IV



in der R¹ die oben zuletzt erwähnte Bedeutung hat, mit der Maßgabe, daß, wenn ein Hydroxy-Substituent in R¹ vorhanden ist, dieser mit einer herkömmlichen Schutzgruppe geschützt ist, und in der Z für eine austauschbare Gruppe steht, mit einer Verbindung mit der folgenden Formel



in der R², Ar, L und Y die in Anspruch 1 angegebenen Bedeutungen haben, umgesetzt wird, mit der Maßgabe, daß, wenn eine Amino-, Alkylamino-, Imino-, Hydroxy- oder Carboxy-Gruppe in R², Ar oder Y vorhanden ist, jede Amino-, Alkylamino-, Imino- und Carboxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt ist und jede Hydroxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt sein kann oder alternativ keine Hydroxy-Gruppe geschützt werden muß;

wonach die Schutzgruppen mit herkömmlichen Mitteln entfernt werden und die R¹-Gruppe, die sich an der 4-Stellung des Chinazolin-Rings befindet, durch Hydrolyse mit einer Base abgespalten wird;

(e) zur Herstellung eines Chinazolins nach Anspruch 1, bei dem Y für eine Gruppe mit der Formel -A-Y¹ steht, in der ein Methylen-Gruppen-Bestandteil in A durch eine Sulfinyl- oder Sulfonyl-Gruppe ersetzt ist, oder bei dem ein Alkylsulfinyl- oder Alkylsulfonyl-Substituent in Y vorhanden ist, eine Verbindung mit der Formel I, bei der Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A durch eine Thio-Gruppe ersetzt ist, oder bei der ein Alkylthio-Substituent in Y vorhanden ist, oxidiert wird; und

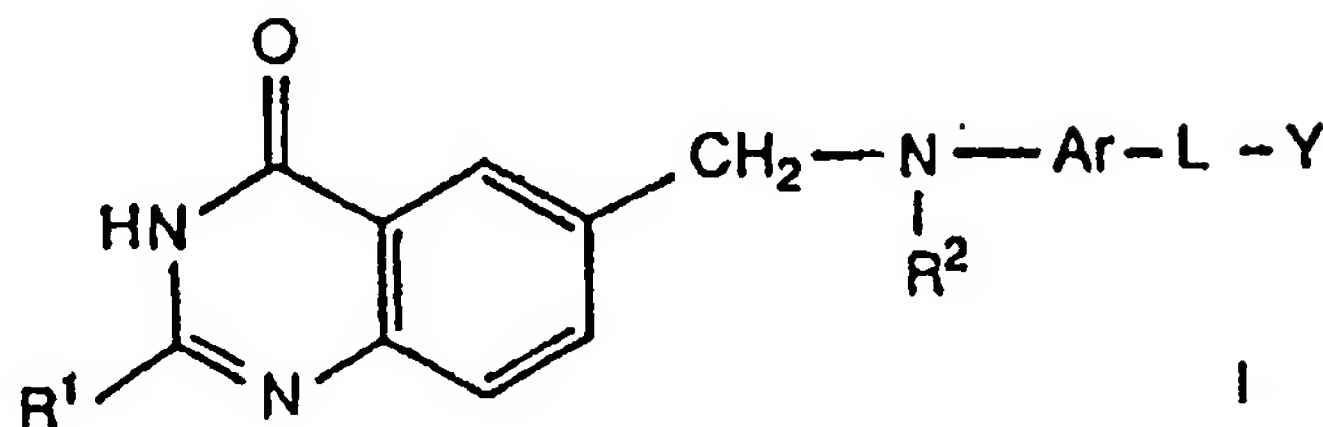
(f) zur Herstellung eines Chinazolins nach Anspruch 1, bei dem ein Carboxy- oder Carboxyalkyl-Substituent in Y vorhanden ist, eine Verbindung mit der Formel I, bei der ein Alkoxy-carbonyl- oder Alkoxy-carbonylalkyl-Substituent in Y vorhanden ist, gespalten wird.

14. Pharmazeutische Zusammensetzung, die ein Chinazolin nach Anspruch 1, oder ein pharmazeutisch geeignetes Salz davon, in Verbindung mit einem pharmazeutisch geeigneten Verdünnungsmittel oder Trägermittel enthält.

15. Verwendung eines Chinazolins nach Anspruch 1, oder eines pharmazeutisch geeigneten Salzes davon, zur Herstellung eines neuen Arzneimittels zur Verwendung für die Erzeugung einer Antitumorwirkung in einem Warmblüter wie dem Menschen.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung eines Chinazolins mit der folgenden Formel I:



in der

R¹ für Wasserstoff oder Amino oder für Alkyl oder Alkoxy steht, die jeweils bis zu 6 Kohlenstoffatome enthalten;

oder in der R¹ für Alkyl mit bis zu 3 Kohlenstoffatomen steht, das einen Hydroxy-Substituenten trägt, oder das einen, zwei oder drei Fluor-Substituenten trägt;

oder in der R¹ für Hydroxyalkoxy mit bis zu 3 Kohlenstoffatomen oder für Alkoxyalkoxy mit bis zu 6 Kohlenstoffatomen steht;

wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen kann, der aus Halogen und aus Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;

R² für Wasserstoff, Alkyl, Alkenyl, Alkynyl, Hydroxyalkyl, Halogenalkyl oder Cyanoalkyl mit jeweils bis zu 6 Kohlenstoffatomen steht,

Ar für Phenylen oder Heterocyclen steht, das unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus Halogen, Hydroxy, Amino und Nitro und aus Alkyl, Alkoxy und Halogenalkyl mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt sind;

L für eine Gruppe mit der Formel -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- oder -CO.O- steht, wobei R³ für Alkyl mit bis zu 6 Kohlenstoffatomen steht; und Y für Aryl mit bis zu 10 Kohlenstoffatomen oder für Heteroaryl oder für ein hydriertes Derivat davon steht; oder in der

Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Alkylen, Cycloalkylen, Alkenylen oder Alkynylen mit jeweils bis zu 6 Kohlenstoffatomen steht, und in der Y¹ für Aryl mit bis zu 10 Kohlenstoffatomen oder für Heteroaryl oder ein hydriertes Derivat davon steht;

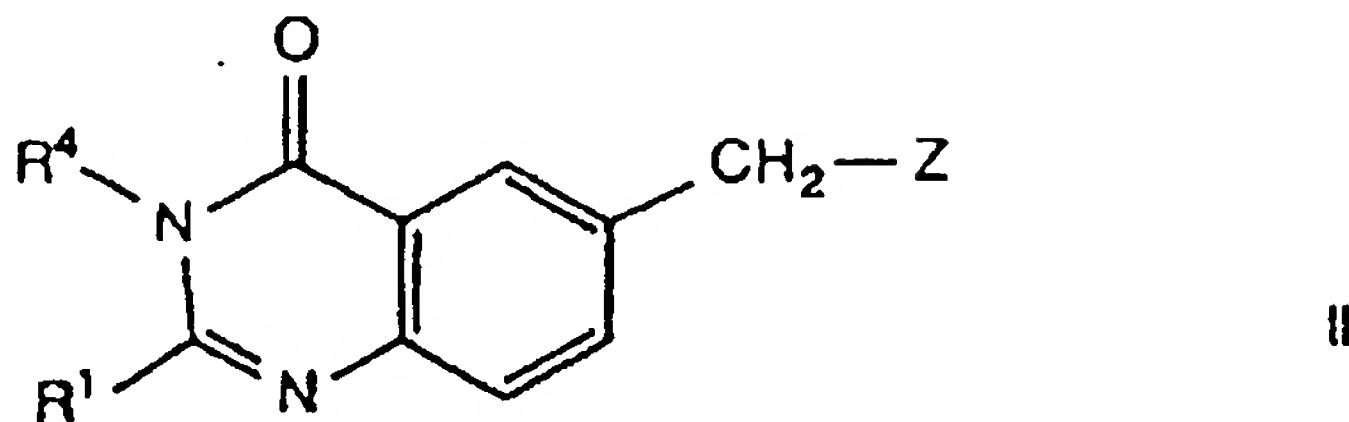
wobei ein Methylen-Gruppen-Bestandteil in A durch eine Oxy-, Thio-, Sulfinyl-, Sulfonyl- oder Imino-Gruppe oder eine Alkylimino-Gruppe mit bis zu 6 Kohlenstoffatomen ersetzt sein kann;

und wobei jede der Aryl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein können oder bis zu drei Substituenten tragen können, die aus folgendem ausgewählt sind: Hydroxy, Oxo, Amino, Nitro, Cyano, Carbamoyl, Sulfamoyl, Carboxy und Halogen, Alkyl, Alkylamino, Dialkylamino, N-Alkylcarbamoyl, N,N-Dialkylcarbamoyl, Alkoxy, Alkanoyloxyalkyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Alkoxy, Halogenalkyl, Hydroxyalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Alkoxyalkyl, Carbamoylalkyl, N-Alkylcarbamoylalkyl und N,N-Dialkylcarbamoylalkyl mit jeweils bis zu 6 Kohlenstoffatomen und Phenyl, Pyridyl und Phenylalkyl mit bis zu 10 Kohlenstoffatomen, wobei jede der Phenyl- oder Phenylalkyl-Gruppen einen Substituenten tragen kann, der aus Halogen und Nitro und Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;

oder eines pharmazeutisch geeigneten Salzes davon; mit der Maßgabe, daß, wenn R¹ für Wasserstoff oder Amino oder für Alkyl mit bis zu 6 Kohlenstoffatomen steht und L für eine Gruppe mit der Formel -CONH- steht, Y dann nicht für Tetrazolyl steht;

dadurch gekennzeichnet, daß:-

(a) eine Verbindung mit der folgenden Formel II



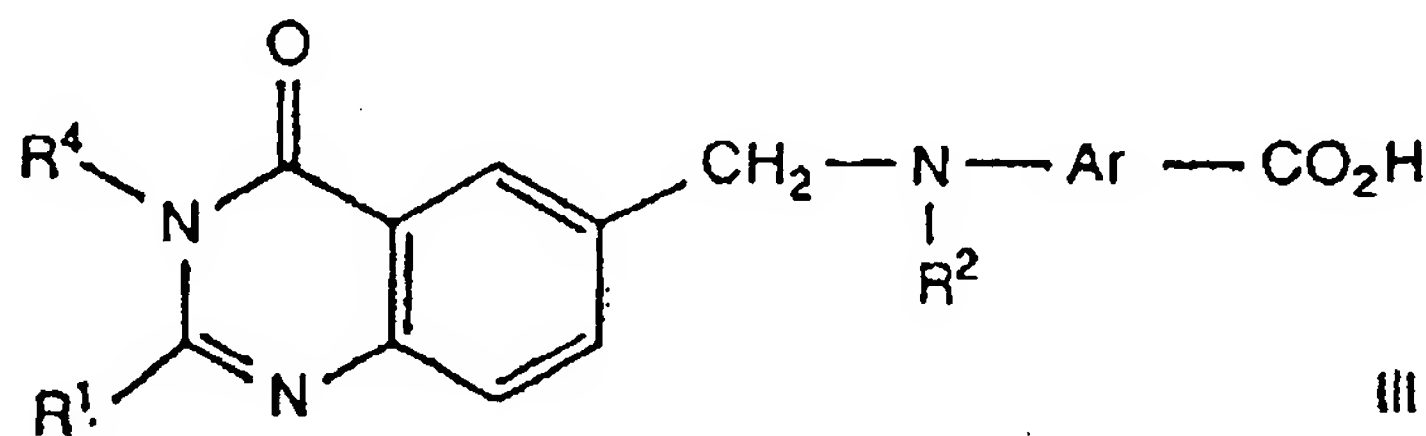
15 in der R¹ die oben angegebene Bedeutung hat, mit der Maßgabe, daß, wenn R¹ für Amino, Hydroxyalkyl oder Hydroxyalkoxy steht, jede Amino- oder Hydroxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt ist, R⁴ für Wasserstoff oder eine Schutzgruppe steht und Z für eine austauschbare Gruppe steht, mit einer Verbindung mit der folgenden Formel:-

HNR²-Ar-L-Y

20 in der R², Ar, L und Y die oben angegebenen Bedeutungen haben, umgesetzt wird, mit der Maßgabe, daß, wenn eine Amino-, Alkylamino-, Imino-, Hydroxy- oder Carboxy-Gruppe in R², Ar oder Y vorhanden ist, jede Amino-, Alkylamino-, Imino- und Carboxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt ist und jede Hydroxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt sein kann oder alternativ keine Hydroxy-Gruppe geschützt werden muß;

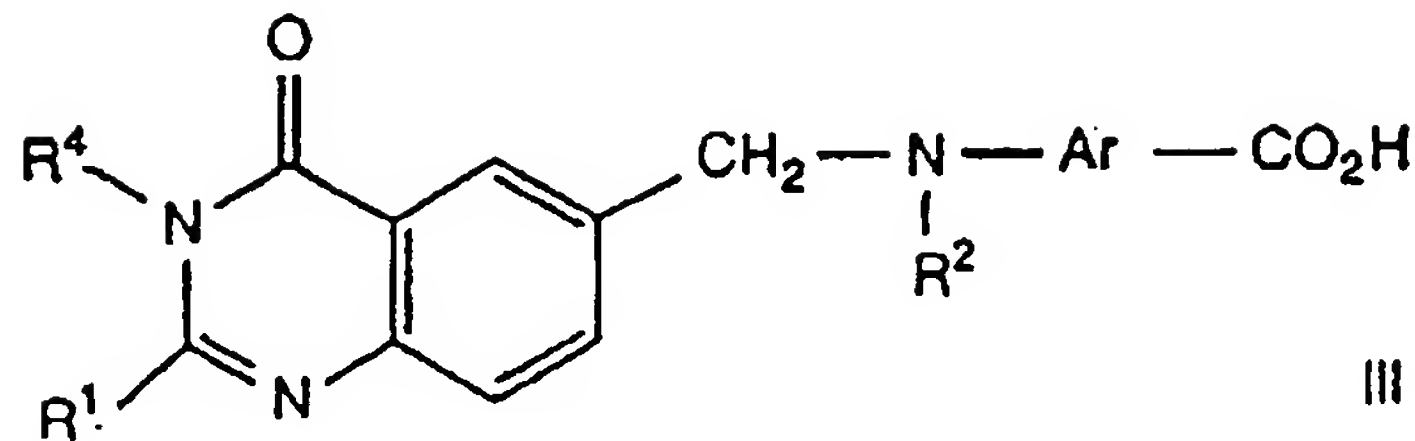
25 wonach jede unerwünschte Schutzgruppe in R¹, R², Ar und Y entfernt wird;

(b) zur Herstellung eines Chinazolins mit der Formel I, bei dem L für eine Gruppe mit der Formel -CONH- oder -CONR³- steht, eine Säure mit der folgenden Formel III, oder ein reaktives Derivat davon



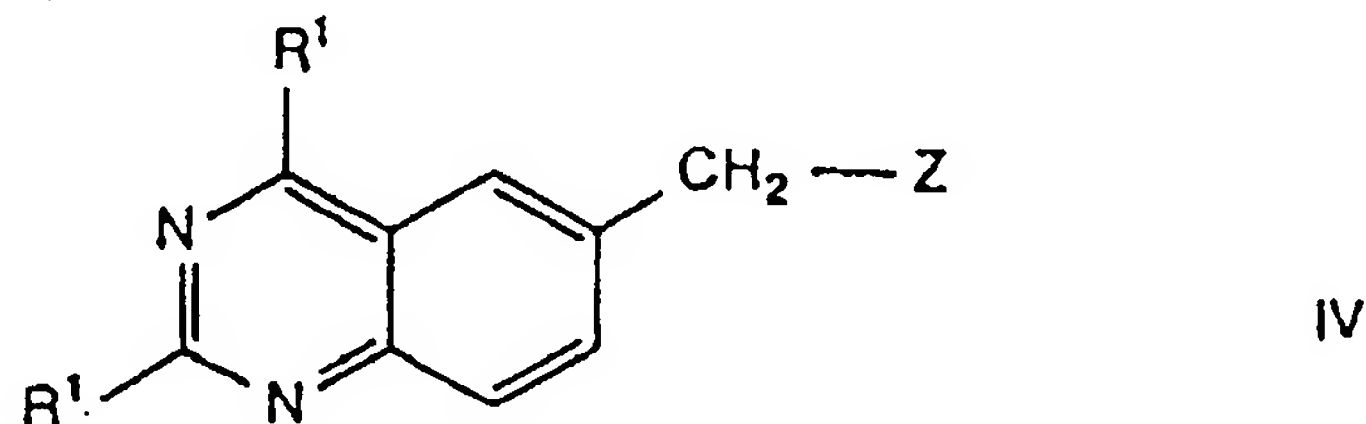
40 mit einer Verbindung mit der Formel H₂N-Y oder R³NH-Y umgesetzt wird, wobei R¹, R², R³, R⁴, Ar und Y die oben angegebenen Bedeutungen haben und jede Amino-, Alkylamino-, Imino- und Carboxy-Gruppe in R¹, Ar und Y mit einer herkömmlichen Schutzgruppe geschützt ist und jede Hydroxy-Gruppe in R¹, R², Ar und Y mit einer herkömmlichen Schutzgruppe geschützt sein kann oder alternativ keine Hydroxy-Gruppe geschützt werden muß; wonach die Schutzgruppen mit herkömmlichen Mitteln entfernt werden;

45 (c) zur Herstellung eines Chinazolins mit der Formel I, bei dem L für eine Gruppe mit der Formel -CO.O- steht, eine Säure mit der folgenden Formel III, oder ein reaktives Derivat davon, in Gegenwart einer geeigneten Base

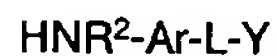


mit einer Verbindung mit der Formel HO-Y umgesetzt wird, wobei R¹, R², R³, R⁴, Ar und Y die oben angegebenen Bedeutungen haben und jede Amino-, Alkylamino-, Imino-, Hydroxy- und Carboxy-Gruppe in R¹, R², Ar und Y mit einer herkömmlichen Schutzgruppe geschützt ist; wonach die Schutzgruppen mit herkömmlichen Mitteln entfernt werden;

(d) zur Herstellung eines Chinazolins mit der Formel I, bei dem R¹ für Alkoxy, Hydroxyalkoxy oder Alkoxyalkoxy steht, eine Verbindung mit der folgenden Formel IV



in der R¹ die oben zuletzt erwähnte Bedeutung hat, mit der Maßgabe, daß, wenn ein Hydroxy-Substituent in R¹ vorhanden ist, dieser mit einer herkömmlichen Schutzgruppe geschützt ist, und in der Z für eine austauschbare Gruppe steht, mit einer Verbindung mit der folgenden Formel



in der R², Ar, L und Y die oben angegebenen Bedeutungen haben, umgesetzt wird, mit der Maßgabe, daß, wenn eine Amino-, Alkylamino-, Imino-, Hydroxy- oder Carboxy-Gruppe in R², Ar oder Y vorhanden ist, jede Amino-, Alkylamino-, Imino- und Carboxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt ist und jede Hydroxy-Gruppe mit einer herkömmlichen Schutzgruppe geschützt sein kann oder alternativ keine Hydroxy-Gruppe geschützt werden muß;

wonach die Schutzgruppen mit herkömmlichen Mitteln entfernt werden und die R¹-Gruppe, die sich an der 4-Stellung des Chinazolin-Rings befindet, durch Hydrolyse mit einer Base abgespalten wird;

(e) zur Herstellung eines Chinazolins mit der Formel I, bei dem Y für eine Gruppe mit der Formel -A-Y¹ steht, in der ein Methylen-Gruppen-Bestandteil in A durch eine Sulfinyl- oder Sulfonyl-Gruppe ersetzt ist, oder bei dem ein Alkylsulfinyl- oder Alkylsulfonyl-Substituent in Y vorhanden ist, eine Verbindung mit der Formel I, bei der Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A durch eine Thio-Gruppe ersetzt ist, oder bei der ein Alkylthio-Substituent in Y vorhanden ist, oxidiert wird; und

(f) zur Herstellung eines Chinazolins mit der Formel I, bei dem ein Carboxy- oder Carboxyalkyl-Substituent in Y vorhanden ist, eine Verbindung mit der Formel I, bei der ein Alkoxy-carbonyl- oder Alkoxy-carbonylalkyl-Substituent in Y vorhanden ist, gespalten wird.

2. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R¹ für Wasserstoff oder Amino oder für Methyl, Ethyl, Methoxy oder Fluormethyl steht; wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann, oder einen weiteren Substituenten tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist; wobei R² für Methyl, Ethyl, Propyl, Prop-2-enyl, Prop-2-ynyl, 2-Hydroxyethyl, 3-Hydroxypropyl, 2-Fluorethyl, 2-Bromethyl oder Cyanomethyl steht; wobei Ar für 1,4-Phenyl, Thienyl, Pyridyl, Pyrimidinyl oder Thiazolyl steht, das unsubstituiert ist, oder einen Substituenten trägt, der aus Fluor, Chlor, Brom, Hydroxy, Amino, Nitro, Methyl,

- Methoxy oder Trifluormethyl ausgewählt ist;
 wobei L für eine Gruppe mit der Formel $-\text{CO.NH}-$, $-\text{CO.NR}^3-$ oder $-\text{CO.O}-$ steht, wobei R^3 für Methyl oder Ethyl steht; und
 wobei Y für Phenyl, 2,5-Dioxopyrrolidinyll oder 2,6-Dioxopiperidinyll steht, oder wobei Y für eine Gruppe mit der Formel $-\text{A-Y}^1$ steht, in der A für Methylen, Ethylen, Ethyliden, Trimethylen, Propyliden, Propylen, Butyliden, Isobutyliden oder Tetramethylen steht, und
 5 Y^1 für Phenyl, Furyl, Thienyl, Pyridyl, Chinolyl, Isochinolyl, Pyrazinyl, Pyrimidinyl, Chinazolinyl, Pyridazinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Oxazolyl, Isoxazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Tetrazolyl oder Hexahydro-2-oxoazepin-1-yl steht;
 10 wobei ein Methylen-Gruppen-Bestandteil in A durch eine Thio-, Sulfinyl-, Sulfonyl oder Imino-Gruppe ersetzt sein kann; und
 wobei jede der Phenyl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein kann oder bis zu drei Substituenten tragen kann, die aus folgendem ausgewählt sind: Hydroxy, Oxo, Amino, Nitro, Cyano, Carbamoyl, Sulfamoyl, Carboxy, Fluor, Chlor, Brom, Methyl, Ethyl, Methylamino, Ethylamino, Dimethylamino, Diethylamino, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Methoxycarbonyl, Ethoxycarbonyl, tert-Butoxycarbonyl, Isobutyryloxymethyl, Pivaloyloxymethyl, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Methoxy, Ethoxy, Trifluormethyl, Carboxymethyl, 1-Carboxyethyl, 2-Carboxyethyl, 3-Carboxypropyl, Carbamoylmethyl, N-Methylcarbamoylmethyl, N,N-Dimethylcarbamoylmethyl, Phenyl, Pyridyl, Benzyl, Phenethyl oder Phenylpropyl, und wobei jede Phenyl-Gruppe in den Substituenten einen Substituenten tragen kann, der aus Fluor, Chlor, Brom, Nitro, Methyl, Ethyl, Methoxy und Ethoxy ausgewählt ist, oder eines pharmazeutisch geeigneten Salzes davon.
3. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R^1 für Amino, Methyl, Methoxy oder Fluormethyl steht;
 25 wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;
 wobei R^2 für Methyl, Ethyl, Prop-2-enyl oder Prop-2-inyl steht;
 wobei Ar für 1,4-Phenyl, Thienyl, Pyridyl oder Thiazolyl steht, das unsubstituiert ist, oder das einen Fluor- oder Nitro-Substituenten trägt;
 30 wobei L für eine Gruppe mit der Formel $-\text{CO.NH}-$ oder $-\text{CO.O}-$ steht; und wobei Y für Phenyl steht, oder wobei Y für eine Gruppe mit der Formel $-\text{A-Y}^1$ steht, in der A für Methylen, Ethylen, Ethyliden, Trimethylen, Propyliden, Propylen oder Isobutyliden steht und Y^1 für Phenyl, 2-Thienyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 3-Chinolyl, 4-Chinolyl, 8-Chinolyl, 2-Pyrimidinyl, 4-Pyrimidinyl, 6-Chinazolinyl, 3-Indolyl, 1-Imidazolyl, 2-Imidazolyl, 4-Imidazolyl, 2-Benzimidazolyl, 2-Thiazolyl, 5-Thiazolyl, 1,2,4-Triazol-1-yl, 1,2,4-Triazol-3-yl oder Tetrazol-5-yl steht, oder wobei Y für Phenylsulfonyl steht; und
 35 wobei jede der Phenyl- oder Heteroaryl-Gruppen unsubstituiert sein kann oder bis zu drei Substituenten tragen kann, die aus folgendem ausgewählt sind: Hydroxy, Oxo, Amino, Nitro, Cyano, Carbamoyl, Carboxy, Fluor, Chlor, Methyl, Ethyl, N-Methylcarbamoyl, N,N-Dimethylcarbamoyl, Methoxycarbonyl, Ethoxycarbonyl, Pivaloyloxymethyl, Methoxy, Trifluormethyl, Carboxymethyl, 1-Carboxyethyl, 2-Carboxyethyl, 3-Carboxypropyl, 4-Pyridyl und Benzyl;
 40 oder eines pharmazeutisch geeigneten Salzes davon.
4. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R^1 für Amino, Methyl oder Methoxy steht;
 45 wobei der Chinazolin-Ring einen Methyl-Substituenten in der 7-Stellung tragen kann;
 wobei R^2 für Methyl, Ethyl oder Prop-2-inyl steht;
 wobei Ar für 1,4-Phenyl oder Thien-2,5-diyl steht oder für Pyrid-2,5-diyl mit der Gruppe $-\text{L-Y}$ in der 2-Stellung oder für 2-Fluor-1,4-phenyl mit der Gruppe $-\text{L-Y}$ in der 1-Stellung steht;
 50 wobei L für eine Gruppe mit der Formel $-\text{CONH}-$ steht; und
 wobei Y für Benzyl oder Phenylsulfonyl steht, das einen Nitro-, Cyano-, Carboxy- oder Trifluormethyl-Substituenten tragen kann, oder wobei Y für Thiazol-5-ylmethyl oder 1,2,3,6-Tetrahydro-2,6-dioxypyrimidin-4-ylmethyl steht, oder wobei Y für 2,3-Dihydro-4-oxochinazolin-6-ylmethyl steht, das einen oder zwei Methyl-Substituenten tragen kann;
 55 oder eines pharmazeutisch geeigneten Salzes davon.
5. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R^1 für Methyl steht;

wobei der Chinazolin-Ring einen Methyl-Substituenten in der 7-Stellung tragen kann;
 wobei R² für Methyl oder Prop-2-ynyl steht;
 wobei Ar für 1,4-Phenylen steht oder für 2-Fluor-1,4-phenylen mit der Gruppe -L-Y in der 1-Stellung;
 wobei L für eine Gruppe mit der Formel -CO.NH- steht; und
 wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen steht und Y¹ für 2-Nitrophenyl, 3-Nitrophenyl, 3-Cyanophenyl, 4-Carboxyphenyl oder 3-Trifluormethylphenyl steht, oder in der Y¹ für 5-Thiazolyl, 2,3-Dihydro-4-oxochinazolin-6-yl, 2,3-Dihydro-2-methyl-4-oxochinazolin-6-yl oder 2,3-Dihydro-2,3-dimethyl-4-oxochinazolin-6-yl steht;
 oder eines pharmazeutisch geeigneten Salzes davon.

6. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins, das aus der folgenden Gruppe von Verbindungen ausgewählt ist:-

p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)benzamid;

p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-trifluormethylbenzyl)benzamid;

p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)benzamid;

p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-methylamino]-o-fluor-N-(3-nitrobenzyl)benzamid;

5-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridin-2-carboxamid;

p-[N-(3,4-Dihydro-2-methoxy-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamid;

p-[N-(2-Amino-3,4-dihydro-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamid;

p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)benzamid und

p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamid;

oder eines pharmazeutisch geeigneten Salzes davon.

7. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R¹ für Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen steht;

oder wobei R¹ für Alkyl mit bis zu 3 Kohlenstoffatomen steht, das einen Hydroxy-Substituenten trägt, oder das einen, zwei oder drei Fluor-Substituenten trägt;

oder wobei R¹ für Hydroxyalkoxy mit bis zu 3 Kohlenstoffatomen steht oder für Alkoxyalkoxy mit bis zu 6 Kohlenstoffatomen;

wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen kann, der aus Halogen und aus Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;

wobei R² für Wasserstoff, Alkyl, Alkenyl, Alkynyl, Hydroxyalkyl, Halogenalkyl oder Cyanoalkyl mit jeweils bis zu 6 Kohlenstoffatomen steht;

wobei Ar für Phenylen oder Heterocyclen steht, das unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus Halogen, Hydroxy und Amino und aus Alkyl, Alkoxy und Halogenalkyl mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt sind;

wobei L für eine Gruppe mit der Formel -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂-O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- oder -CO.O- steht, wobei R³ für Alkyl mit bis zu 6 Kohlenstoffatomen steht; und

wobei Y für Aryl mit bis zu 10 Kohlenstoffatomen steht, oder für Heteroaryl oder ein hydriertes Derivat davon; oder

wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Alkylen, Cycloalkylen, Alkenylen oder Alkinylen mit jeweils bis zu 6 Kohlenstoffatomen steht, und Y¹ für Aryl mit bis zu 10 Kohlenstoffatomen, oder für Heteroaryl oder ein hydriertes Derivat davon steht;

wobei ein Methylen-Gruppen-Bestandteil in A durch eine Oxy-, Thio-, Sulfinyl-, Sulfonyl- oder Imino-Gruppe oder eine Alkylimino-Gruppe mit bis zu 6 Kohlenstoffatomen ersetzt sein kann; und

wobei jede der Aryl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein können oder einen oder zwei Substituenten tragen können, die aus folgendem ausgewählt sind:

- Hydroxy, Amino, Nitro, Cyano, Carbamoyl, Carboxy und Halogen, Alkyl, Alkylamino, Dialkylamino, N-Alkylcarbamoyl, N,N-Dialkylcarbamoyl, Alkoxy-carbonyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Alkoxy, Halogenalkyl, Hydroxyalkyl, Aminoalkyl, Alkylaminoalkyl, Dialkylaminoalkyl, Carboxyalkyl, Alkoxy-carbo-
 5 nylalkyl, Carbamoylalkyl, N-Alkylcarbamoylalkyl und N,N-Dialkylcarbamoylalkyl mit jeweils bis zu 6 Kohlenstoffatomen und Phenyl und Phenylalkyl mit bis zu 10 Kohlenstoffatomen, wobei jede der Phenyl-Gruppen einen Substituenten tragen kann, der aus Halogen und aus Alkyl und Alkoxy mit jeweils bis zu 3 Kohlenstoffatomen ausgewählt ist;
 oder eines pharmazeutisch geeigneten Salzes davon;
 mit der Maßgabe, daß, wenn R¹ für Alkyl mit bis zu 6 Kohlenstoffatomen steht, der Chinazolin-Ring
 10 keine, weiteren Substituenten trägt oder einen weiteren Substituenten trägt, der aus Halogen und Alkyl mit bis zu 3 Kohlenstoffatomen ausgewählt ist, R² für Alkyl, Alkenyl oder Alkynyl mit jeweils bis zu 6 Kohlenstoffatomen steht, Ar für Phenylen steht, das unsubstituiert ist oder einen oder zwei Substituen-
 ten trägt, die aus Halogen, Hydroxy und Amino ausgewählt sind, und L für eine Gruppe mit der Formel -CONH- steht, Y dann nicht für Tetrazol-5-yl steht.
- 15 8. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel 1, wobei R¹ für Methyl, Ethyl, Methoxy oder Fluormethyl steht;
 wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;
 20 wobei R² für Wasserstoff, Methyl, Ethyl, Propyl, Prop-2-enyl, Prop-2-ynyl, 2-Hydroxyethyl, 3-Hydroxypropyl, 2-Fluorethyl, 2-Bromomethyl oder Cyanomethyl steht;
 wobei Ar für 1,4-Phenylen, Thienylen, Pyridylen, Pyrimidinylen, Thiazolylen oder Thiadiazolylen steht, das unsubstituiert ist oder einen oder zwei Substituenten trägt, die aus Fluor, Chlor, Brom, Hydroxy, Amino, Methyl, Methoxy und Trifluormethyl ausgewählt, sind;
 25 wobei L für eine Gruppe mit der Formel -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO, -CH=CH-, -CH₂O-, -CO.CH₂- oder -CO.O- steht, wobei R³ für Methyl oder Ethyl steht; und
 wobei Y für Phenyl, Naphthyl, Pyridyl, Chinolyl, Isochinolyl, Pyrimidinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Oxazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Thiadiazolyl oder Tetrazolyl steht; oder
 30 wobei Y für eine Gruppe mit der Formel -A-Y¹ steht, in der A für Methylen, Ethylen, Ethyleniden, Trimethylen, Propylen, 1-Isopropylethylen oder Tetramethylen steht und Y¹ für Phenyl, Naphthyl, Pyridyl, Chinolyl, Isochinolyl, Pyrazinyl, Pyrimidinyl, Pyridazinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Oxazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Thiadiazolyl oder Tetrazolyl steht;
 35 wobei ein Methylen-Gruppen-Bestandteil in A durch eine Oxy-, Thio-, Sulfinyl- oder Sulfonyl-Gruppe ersetzt sein kann; und
 wobei jede der Aryl- oder Heteroaryl-Gruppen, oder die hydrierten Derivate davon, unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus folgendem ausgewählt sind: Hydroxy, Amino, Nitro, Cyano, Carbamoyl, Carboxy, Fluor, Chlor, Brom, Methyl, Ethyl, Methylamino, Ethylamino,
 40 Dimethylamino, Diethylamino, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Methoxycarbonyl, Ethoxycarbonyl, tert-Butoxycarbonyl, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Isopropylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Isopropylsulfonyl, Methoxy, Ethoxy, Trifluormethyl, Carboxymethyl, 2-Carboxyethyl, Carbamoylmethyl, N-Methylcarbamoylmethyl, N,N-Dimethylcarbamoylmethyl, Phenyl, Benzyl, Phenethyl oder Phenylpropyl, und wobei jede der
 45 Phenyl-Gruppen einen Substituenten tragen kann, der aus Fluor, Chlor, Brom, Methyl, Ethyl, Methoxy und Ethoxy ausgewählt ist;
 oder eines pharmazeutisch geeigneten Salzes davon;
 mit der Maßgabe, daß, wenn R¹ für Methyl oder Ethyl steht, der Chinazolin-Ring keine weiteren Substituenten trägt oder einen weiteren Substituenten trägt, der aus Fluor, Chlor und Methyl ausge-
 50 wählt ist, R² für Methyl, Ethyl, Propyl, Prop-2-enyl oder Prop-2-ynyl steht, Ar für 1,4-Phenylen steht, das unsubstituiert ist oder einen oder zwei Substituenten trägt, die aus Fluor, Chlor, Brom, Hydroxy und Amino, ausgewählt sind, und
 L für eine Gruppe mit der Formel -CONH- steht, Y dann nicht für Tetrazol-5-yl steht.
- 55 9. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R¹ für Methyl, Ethyl, Methoxy oder Fluormethyl steht;
 wobei der Chinazolin-Ring keine weiteren Substituenten tragen kann oder einen weiteren Substituenten tragen;

- kann, der aus Fluor, Chlor, Methyl und Methoxy ausgewählt ist;
 wobei R^2 für Wasserstoff, Methyl, Ethyl, Propyl, Prop-2-ynyl, Prop-2-ynyl, 2-Hydroxyethyl, 3-Hydroxypropyl, 2-Fluorethyl, 2-Bromethyl oder Cyanomethyl steht;
 wobei Ar für 1,4-Phenylen, Thien-2,5-diyl, Pyrid-2,5-diyl oder Thiazol-2,5-diyl steht, das unsubstituiert ist oder das einen oder zwei Substituenten trägt, die aus Fluor, Chlor, Hydroxy, Amino und Methyl ausgewählt sind;
 wobei L für eine Gruppe mit der Formel $-CO.NH-$, $-CO.NR^3-$ oder $-CO.O-$ steht, wobei R^3 für Methyl oder Ethyl steht; und
 wobei Y für Phenyl, Pyridyl, Pyrimidinyl, Imidazolyl, Thiazolyl oder 1,2,3-Triazolyl steht; oder
 wobei Y für eine Gruppe mit der Formel $-A-Y^1$ steht, in der A für Methylen, Ethylen, Ethylen oder Trimethylen steht und Y^1 für Phenyl, Naphthyl, Pyridyl, Chinolyl, Isochinolyl, Pyrimidinyl, Indolyl, Imidazolyl, Benzimidazolyl, Pyrazolyl, Indazolyl, Thiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, Thiadiazolyl oder Tetrazolyl steht; und
 wobei jede der Aryl- oder Heteroaryl-Gruppen unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus Amino, Nitro, Fluor, Methyl, Carbamoyl, N-Methylcarbamoyl, N,N-Dimethylcarbamoyl, Methoxycarbonyl, Ethoxycarbonyl, Methylsulfinyl, Methylsulfonyl, Methoxy, Trifluormethyl oder Benzyl ausgewählt sind;
 oder eines pharmazeutisch geeigneten Salzes davon.
10. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R^1 für Methyl steht; wobei R^2 für Wasserstoff, Methyl, Ethyl, Prop-2-ynyl oder 2-Fluorethyl steht;
 wobei Ar für 1,4-Phenylen oder Thien-2,5-diyl oder für Pyrid-2,5-diyl oder für Thiazol-2,5-diyl mit der Gruppe $-L-Y$ jeweils in der 2-Stellung oder für 2-Fluor-1,4-Phenylen mit der Gruppe $-L-Y$ in der 1-Stellung steht;
 wobei L für eine Gruppe mit der Formel $-CO.NH-$, $-CO.NR^3-$ oder $-CO.O-$ steht, wobei R^3 für Methyl oder Ethyl steht; und
 worin Y für Phenyl steht; oder
 wobei Y für eine Gruppe mit der Formel $-A-Y^1$ steht, in der A für Methylen, Ethylen, Ethylen oder Trimethylen steht und Y^1 für Phenyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 1-Isochinolyl, 3-Isochinolyl, 4-Isochinolyl, 2-Pyrimidinyl, 4-Pyrimidinyl, 5-Pyrimidinyl, 2-Indolyl, 3-Indolyl, 1-Imidazolyl, 2-Imidazolyl, 2-Benzimidazolyl, 1-Pyrazolyl, 3-Pyrazolyl, 4-Pyrazolyl, 3-Indazolyl, 2-Thiazolyl, 4-Thiazolyl, 5-Thiazolyl, 1,2,3-Triazol-4-yl, 1,2,4-Triazol-3-yl, 1,2,4-Triazol-4-yl, 1,2,4-Triazol-1-yl, 2-Thiadiazolyl oder 5-Tetrazolyl steht; und
 wobei jede der Aryl- oder Heteroaryl-Gruppen unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die aus Amino, Nitro, Carbamoyl, Fluor, Methyl, Ethoxycarbonyl, Methylsulfinyl, Methylsulfonyl, Methoxy, Trifluormethyl oder Benzyl ausgewählt sind;
 oder eines pharmazeutisch geeigneten Salzes davon.
11. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins mit der Formel I, wobei R^1 für Methyl steht; wobei R^2 für Methyl, Ethyl oder Prop-2-ynyl steht;
 wobei Ar für 1,4-Phenylen oder Thien-2,5-diyl steht, oder für Pyrid-2,5-diyl oder Thiazol-2,5-diyl mit der Gruppe $-L-Y$ jeweils in der 2-Stellung oder für 2-Fluor-1,4-phenylen mit der Gruppe $-L-Y$ in der 1-Stellung;
 wobei L für eine Gruppe mit der Formel $-CO.NH-$ steht; und
 wobei Y für eine Gruppe mit der Formel $-A-Y^1$ steht, in der A für Methylen oder Ethylen steht und Y^1 für 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 3-Indolyl oder 1,2,4-Triazol-1-yl steht, oder in der Y^1 für Phenyl steht, das unsubstituiert sein kann oder einen Substituenten tragen kann, der aus Amino, Nitro, Ethoxycarbonyl oder Trifluormethyl ausgewählt ist;
 oder eines pharmazeutisch geeigneten Salzes davon.
12. Verfahren nach Anspruch 1 zur Herstellung eines Chinazolins, das aus der folgenden Gruppe von Verbindungen ausgewählt ist:-
 N-Benzyl-p-[N-(3,4-dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamid;
 p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)-benzamid;
 p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylmethyl)-benzamid;
 p-[N-(3,4-Dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylmethyl)-

benzamid und

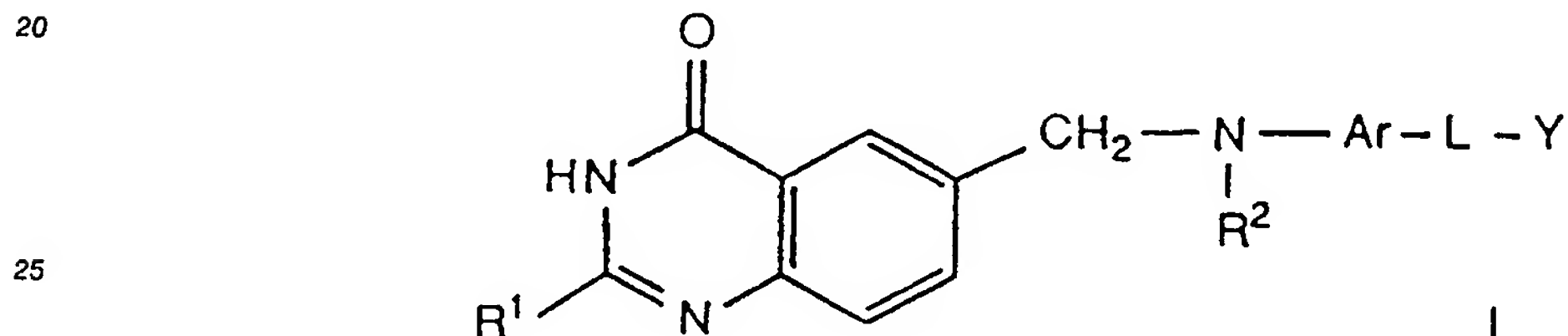
N-Benzylimidazol-2-ylmethyl-p-[N-(3,4-dihydro-2-methyl-4-oxochinazolin-6-ylmethyl)-N-ethylamino]-benzoat.

- 5 13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, dadurch **gekennzeichnet**, daß ein wie in einem der Ansprüche 1 bis 12 definiertes Chinazolin, oder ein pharmazeutisch geeignetes Salz davon, und ein pharmazeutisch geeignetes Verdünnungsmittel oder Trägermittel miteinander vermischt werden.
- 10 14. Verwendung eines Chinazolins wie in einem der Ansprüche 1 bis 12 definiert, oder eines pharmazeutisch geeigneten Salzes davon, zur Herstellung eines neuen Arzneimittels zur Verwendung für die Erzeugung einer Antitumorwirkung in einem Warmblüter wie dem Menschen.

Revendications

15 **Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE**

1. Quinazoline de formule I



30 dans laquelle R¹ représente l'hydrogène ou un groupe amino, ou bien un groupe alkyle ou alkoxy ayant chacun jusqu'à 6 atomes de carbone ;

ou R¹ représente un groupe alkyle ayant jusqu'à 3 atomes de carbone qui porte un substituant hydroxy, ou bien qui porte 1, 2 ou 3 substituants fluoro ;

ou bien R¹ représente un groupe hydroxyalkoxy ayant jusqu'à 3 atomes de carbone ou alkoxyalkoxy ayant jusqu'à 6 atomes de carbone ;

35 le noyau quinazoline pouvant ne porter aucun substituant supplémentaire ou bien pouvant porter un substituant supplémentaire choisi entre un groupe halogéno ainsi qu'un groupe alkyle et un groupe alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

R² représente l'hydrogène, un groupe alkyle, alcényle, alcynyle, hydroxyalkyle, halogénalkyle ou cyanoalkyle ayant chacun jusqu'à 6 atomes de carbone ;

40 Ar représente un groupe phénylène ou hétérocyclène qui peut être non substitué ou qui peut porter un ou deux substituants choisis entre des groupes halogéno, hydroxy, amino et nitro, et entre des groupes alkyle, alkoxy et halogénalkyle ayant chacun jusqu'à 3 atomes de carbone ;

L représente un groupe de formule -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- ou -CO.O-, dans laquelle R³ représente un groupe alkyle ayant jusqu'à 6 atomes de carbone ; et

45 Y représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou bien un de ses dérivés hydrogénés ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe alkylène, cycloalkylène, alcénylène ou alcynylène ayant chacun jusqu'à 6 atomes de carbone, et Y¹ représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou hétéroaryle ou bien un de ses dérivés hydrogénés ; un groupe méthylène constitutif dans le groupe A pouvant être remplacé par un groupe oxy, thio, sulfinyle, sulfonyle ou imino ou un groupe alkylimino ayant jusqu'à 6 atomes de carbone ;

55 chacun desdits groupes aryle ou hétéroaryle, ou de leurs dérivés hydrogénés, pouvant être non substitué ou pouvant porter jusqu'à trois substituants choisis entre des groupes hydroxy, oxo, amino, nitro, cyano, carbamoyle, sulfamoyle, carboxy et halogéno, entre des groupes alkyle, alkylamino, dialkylamino, N-alkylcarbamoyle, N,N-dialkylcarbamoyle, alkoxycarbonyl, alcanoyloxyalkyle, alkylthio, alkylsulfinyle, alkylsulfonyl, alkoxy, halogénalkyle, hydroxyalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxyalkyle, alkoxycarbonylalkyle, carbamoylalkyle, N-alkylcarbamoylalkyle et N,N-

dialkylcarbamoyalkyle ayant chacun jusqu'à 6 atomes de carbone, et entre des groupes phényle, pyridyle et phénylalkyle ayant jusqu'à 10 atomes de carbone, et chacun desdits groupes phényle ou phénylalkyle pouvant porter un substituant choisi entre des groupes halogéno et nitro, et entre des groupes alkyle et alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

5 ou un de ses sels pharmaceutiquement acceptables ;

sous réserve que, lorsque R¹ représente l'hydrogène ou un groupe amino, ou bien un groupe alkyle ayant jusqu'à 6 atomes de carbone, et L représente un groupe de formule -CONH-, Y ne représente alors pas un groupe tétrazolyle.

10 2. Quinazoline de formule I suivant la revendication 1, dans laquelle

R¹ représente l'hydrogène ou un groupe amino, ou bien un groupe méthyle, éthyle, méthoxy ou fluorométhyle ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

15 R² représente un groupe méthyle, éthyle, propyle, prop-2-ényle, prop-2-ynyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-fluoréthyle, 2-bromoéthyle ou cyanométhyle ;

Ar représente un groupe 1,4-phénylène, thiénylène, pyridylène, pyrimidinylène ou thiazolylène qui est non substitué ou qui porte un substituant choisi entre les groupes fluoro, chloro, bromo, hydroxy, amino, nitro, méthyle, méthoxy et trifluorométhyle ;

20 L représente un groupe de formule -CO.NH-, -CO.NR³- ou -CO.O-, dans laquelle R³ représente un groupe méthyle ou éthyle : et

Y représente un groupe phényle, 2,5-dioxopyrrolidinyle ou 2,6-dioxopipéridinyle, ou bien Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène, triméthylène, propylidène, propylène, butylidène, isobutylidène ou tétraméthylène et Y¹ représente un groupe phényle, furyle, thiényle, pyridyle, quinolyle, isoquinolyle, pyrazinyle, pyrimidinyle, quinazolinyle, pyridazinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, oxazolyle, isoxazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, tétrazolyle ou hexahydro-2-oxoazépin-1-yle ;

un groupe méthylène constitutif dans A pouvant être remplacé par un groupe thio, sulfinyle, sulfonyle ou imino : et

30 chacun desdits groupes phényle ou hétéroaryle, ou de leurs dérivés hydrogénés, peut être non substitué ou bien peut porter jusqu'à trois substituants choisis entre les groupes hydroxy, oxo, amino, nitro, cyano, carbamoyle, sulfamoyle, carboxy, fluoro, chloro, bromo, méthyle, éthyle, méthylamino, éthylamino, diméthylamino, diéthylamino, N-méthylcarbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, tertio-butyoxycarbonyle, isobutyryloxyméthyle, pivaloyloxyméthyle, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, méthylsulfonyle, éthylsulfonyle, méthoxy, éthoxy, trifluorométhyle, carboxyméthyle, 1-carboxyéthyle, 2-carboxyéthyle, 3-carboxypropyle, carbamoylméthyle, N-méthylcarbamoylméthyle, N,N-diméthylcarbamoylméthyle, phényle, pyridyle, benzyle, phénéthyle ou phénylpropyle, et n'importe quel groupe phényle à l'intérieur desdits substituants peut porter un substituant choisi entre les groupes fluoro, chloro, bromo, nitro, méthyle, éthyle, méthoxy et éthoxy ;

40 ou un de ses sels pharmaceutiquement acceptables.

3. Quinazoline de formule I suivant la revendication 1,

dans laquelle R¹ représente un groupe amino, méthyle, méthoxy ou fluorométhyle ;

45 le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

R² représente un groupe méthyle, éthyle, prop-2-ényle ou prop-2-ynyle ;

Ar représente un groupe 1,4-phénylène, thiénylène, pyridylène ou thiazolylène qui est non substitué ou qui porte un substituant fluoro ou nitro ;

50 L représente un groupe de formule -CO.NH- ou -CO.O- ; et

Y représente un groupe phényle, ou bien Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène, triméthylène, propylidène, propylène ou isobutylidène, et Y¹ représente un groupe phényle, 2-thiényle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 3-quinolyle, 4-quinolyle, 8-quinolyle, 2-pyrimidinyle, 4-pyrimidinyle, 6-quinazolinyle, 3-indolyle, 1-imidazolyle, 2-imidazolyle, 4-imidazolyle, 2-benzimidazolyle, 2-thiazolyle, 5-thiazolyle, 1,2,4-triazole-1-yle, 1,2,4-triazole-3-yle ou tétrazole-5-yle ou bien Y représente un groupe phénylsulfonyle ; et

55 chacun desdits groupes phényle ou hétéroaryle peut être non substitué ou peut porter jusqu'à trois substituants choisis entre les groupes hydroxy, oxo, amino, nitro, cyano, carbamoyle, carboxy, fluoro,

chloro, méthyle, éthyle, N-méthylcarbamoyle, N,N-diméthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, pivaloyloxyméthyle, méthoxy, trifluorométhyle, carboxyméthyle, 1-carboxyéthyle, 2-carboxyéthyle, 3-carboxypropyle, 4-pyridyle et benzyle ;

ou un de ses sels pharmaceutiquement acceptables.

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4. Quinazoline de formule I suivant la revendication 1, dans laquelle

R¹ représente un groupe amino, méthyle ou méthoxy ;

le noyau quinazoline peut porter un substituant méthyle en position 7 ;

R² représente un groupe méthyle, éthyle ou prop-2-ynyle ;

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Ar représente un groupe 1,4-phénylène ou thién2,5-diyle, ou bien représente un groupe pyrid-2,5-diyle avec le groupe -L-Y en position 2, ou représente un groupe 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CONH- ;

15

et Y représente un groupe benzyle ou phénylsulfonyl qui peut porter un substituant nitro, cyano, carboxy ou trifluorométhyle, ou Y représente un groupe thiazole-5-ylméthyle ou 1,2,3,6-tétrahydro-2,6-dioxypyrimidin-4-ylméthyle, ou bien Y représente un groupe 2,3-dihydro-4-oxoquinazolin-6-ylméthyle qui peut porter un ou deux substituants méthyle ;

ou un de ses sels pharmaceutiquement acceptables.

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5. Quinazoline de formule I suivant la revendication 1, dans laquelle R¹ représente un groupe méthyle ; le noyau quinazoline peut porter un substituant méthyle en position 7 ; R² représente un groupe méthyle ou prop-2-ynyle ; Ar représente un groupe 1,4-phénylène, ou 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CO.NH- ; et

25

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène et Y¹ représente un groupe 2-nitrophényle, 3-nitrophényle, 3-cyanophényle, 4-carboxyphényle ou 3-trifluorométhylphényle ou Y¹ représente un groupe 5-thiazolyle, 2,3-dihydro-4-oxoquinazolin-6-yle, 2,3-dihydro-2-méthyl-4-oxoquinazolin-6-yle ou 2,3-dihydro-2,3-diméthyl-4-oxoquinazolin-6-yle ;

ou un de ses sels pharmaceutiquement acceptables.

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6. Quinazoline de formule I suivant la revendication 1, choisie dans le groupe de composés :

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)benzamide ;

35

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-trifluorométhylbenzyl)benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-méthylamino]-o-fluoro-N-(3-nitrobenzyl)benzamide ;

40

5-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide ;

p-[N-(3,4-dihydro-2-méthoxy-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide ;

45

p-[N-(2-amino-3,4-dihydro-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)benzamide, et

p-[N-(3,4-dihydro-2,7-diméthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)benzamide ;

50

ou un de ses sels pharmaceutiquement acceptables.

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7. Quinazoline de formule I suivant la revendication 1, dans laquelle R¹ représente un groupe alkyle ou alkoxy ayant chacun jusqu'à 6 atomes de carbone ; ou R¹ représente un groupe alkyle ayant jusqu'à 3 atomes de carbone qui porte un substituant hydroxy, ou qui porte un, deux ou trois substituants fluoro ; ou bien R¹ représente un groupe hydroxyalkoxy ayant jusqu'à 3 atomes de carbone ou alkoxyalkoxy ayant jusqu'à 6 atomes de carbone ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre un groupe halogéno et un groupe alkyle et un groupe alkoxy

ayant chacun jusqu'à 3 atomes de carbone ;

R² représente l'hydrogène, un groupe alkyle, alcényle, alcynyle, hydroxyalkyle, halogénalkyle ou cyanoalkyle ayant chacun jusqu'à 6 atomes de carbone ;

Ar représente un groupe phénylène ou hétérocyclène qui peut être non substitué ou qui peut porter un ou deux substituants choisis entre des groupes halogéno, hydroxy et amino, et entre des groupes alkyle, alkoxy et halogénalkyle ayant chacun jusqu'à 3 atomes de carbone ;

L représente un groupe de formule -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- ou -CO.O-, dans laquelle R³ représente un groupe alkyle ayant jusqu'à 6 atomes de carbone ; et

Y représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou bien un de leurs dérivés hydrogénés ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe alkylène, cycloalkylène, alcénylène ou alcynylène ayant chacun jusqu'à 6 atomes de carbone, et Y¹ représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou bien un de leurs dérivés hydrogénés ;

un groupe méthylène constitutif dans A peut être remplacé par un groupe oxy, thio, sulfinyle, sulfonyl ou imino ou un groupe alkylimino ayant jusqu'à 6 atomes de carbone ; et

chacun desdits groupes aryle ou hétéroaryle, ou de leurs dérivés hydrogénés, peut être non substitué ou peut porter un ou deux substituants choisis entre des groupes hydroxy, amino, nitro, cyano, carbamoyl, carboxy et halogéno, entre des groupes alkyle, alkylamino, dialkylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, alkoxy-carbonyl, alkylthio, alkylsulfinyle, alkylsulfonyl, alkoxy, halogénalkyle, hydroxyalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxyalkyle, alkoxy-carbonylalkyle, carbamoylalkyle, N-alkylcarbamoylalkyle et N,N-dialkylcarbamoylalkyle ayant chacun jusqu'à 6 atomes de carbone et entre des groupes phényle et phénylalkyle ayant jusqu'à 10 atomes de carbone, et chacun desdits groupes phényle peut porter un substituant choisi entre un substituant halogéno et un substituant alkyle et un substituant alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

ou un de ses sels pharmaceutiquement acceptables ;

sous réserve que, lorsque R¹ représente un groupe alkyle ayant jusqu'à 6 atomes de carbone, le noyau quinazoline ne porte aucun substituant supplémentaire ou bien porte un substituant supplémentaire choisi entre un groupe halogéno et un groupe alkyle ayant jusqu'à 3 atomes de carbone, R² représente un groupe alkyle, alcényle ou

alcynyle ayant chacun jusqu'à 6 atomes de carbone,

Ar représente un groupe phénylène qui est non substitué ou qui porte un ou deux substituants choisis entre des groupes halogéno, hydroxy et amino, et

L représente un groupe de formule -CONH-, alors Y ne représente pas un groupe tétrazole-5-yle.

8. Quinazoline de formule I suivant la revendication 1, dans laquelle R¹ représente un groupe méthyle, éthyle, méthoxy ou fluorométhyle ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

R² représente l'hydrogène, un groupe méthyle, éthyle, propyle, prop-2-ényle, prop-2-ynyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-fluoroéthyle, 2-bromoéthyle ou cyanométhyle ;

Ar représente un groupe 1,4-phénylène, thiénylène, pyridylène, pyrimidinylène, thiazolylène ou thiadiazolylène qui est non substitué ou qui porte un ou deux substituants choisis entre les groupes fluoro, chloro, bromo, hydroxy, amino, méthyle, méthoxy et trifluorométhyle ; L représente un groupe de formule -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -CO.CH₂- ou -CO.O-, dans laquelle R³ représente un groupe méthyle ou éthyle ; et

Y représente un groupe phényle, naphtyle, pyridyle, quinolyle, isoquinolyle, pyrimidinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, oxazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, thiadiazolyle ou tétrazolyle ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène, triméthylène, propylidène, propylène, 1-isopropyléthylène ou tétraméthylène et Y¹ représente un groupe phényle, naphtyle, pyridyle, quinolyle, isoquinolyle, pyrazinyle, pyrimidinyle, pyridazinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, oxazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, thiadiazolyle ou tétrazolyle ;

un groupe méthylène constitutif dans A peut être remplacé par un groupe oxy, thio, sulfinyle ou sulfonyl ; et

chacun desdits groupes aryle ou hétéroaryle, ou de leurs dérivés hydrogénés, peut être non

- substitué ou peut porter un ou deux substituants choisis entre les groupes hydroxy, amino, nitro, cyano, carbamoyle, carboxy, fluoro, chloro, bromo, méthyle, éthyle, méthylamino, éthylamino, diméthylamino, diéthylamino, N-méthylcarbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, tertio-butoxycarbonyle, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, isopropylsulfinyle, méthylsulfonyle, éthylsulfonyle, isopropylsulfonyle, méthoxy, éthoxy, trifluorométhyle, carboxyméthyle, 2-carboxyéthyle, carbamoylméthyle, N-méthylcarbamoylméthyle, N,N-diméthylcarbamoylméthyle, phényle, benzyle, phénéthyle et phénylpropyle, et chacun desdits groupes phényle peut porter un substituant choisi entre les groupes fluoro, chloro, bromo, méthyle, éthyle, méthoxy et éthoxy ;
- ou un de ses sels pharmaceutiquement acceptables ;
- sous réserve que, lorsque R¹ représente un groupe méthyle ou éthyle, le noyau quinazoline ne porte aucun substituant supplémentaire ou bien porte un substituant supplémentaire choisi entre les groupes fluoro, chloro et méthyle ;
- R² représente un groupe méthyle, éthyle, propyle, prop-2-ényle ou prop-2-ynyle,
- Ar représente un groupe 1,4-phénylène qui est non substitué ou qui porte un ou deux substituants choisis entre les groupes fluoro, chloro, bromo, hydroxy et amino, et
- L représente un groupe de formule -CONH-, alors Y ne représente pas un groupe tétrazole-5-yle.
9. Quinazoline de formule I suivant la revendication 1, dans laquelle R¹ représente un groupe méthyle, éthyle, méthoxy ou fluorométhyle ;
- le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;
- R² représente l'hydrogène, un groupe méthyle, éthyle, propyle, prop-2-ényle, prop-2-ynyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-fluoroéthyle, 2-bromoéthyle ou cyanométhyle ;
- Ar représente un groupe 1,4-phénylène, thién-2,5-diyle, pyrid-2,5-diyle ou thiazole-2,5-diyle qui est non substitué ou bien qui porte un ou deux substituants choisis entre les groupes fluoro, chloro, hydroxy, amino et méthyle ;
- L représente un groupe de formule -CO.NH-, -CO.NR³- ou -CO.O-, dans laquelle R³ représente un groupe méthyle ou éthyle ; et
- Y représente un groupe phényle, pyridyle, pyrimidinyle, imidazolyle, thiazolyle ou 1,2,3-triazolyle ;
- ou
- Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène ou triméthylène et Y¹ représente un groupe phényle, naphtyle, pyridyle, quinolyle, isoquinolyle, pyrimidinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, thiadiazolyle ou tétrazolyle ; et
- chacun desdits groupes aryle ou hétéroaryle peut être non substitué ou bien peut porter un ou deux substituants choisis entre les groupes amino, nitro, fluoro, méthyle, carbamoyle, N-méthylcarbamoyle, N,N-diméthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, méthylsulfinyle, méthylsulfonyle, méthoxy, trifluorométhyle et benzyle ;
- ou un de ses sels pharmaceutiquement acceptables.
10. Quinazoline de formule I suivant la revendication 1, dans laquelle R¹ représente un groupe méthyle ; R² représente l'hydrogène, un groupe méthyle, éthyle, prop-2-ynyle ou 2-fluoréthyle ;
- Ar représente un groupe 1,4-phénylène ou thién-2,5-diyle, ou bien représente un groupe pyrid-2,5-diyle ou thiazole-2,5-diyle, chacun avec le groupe -L-Y en position 2, ou représente un groupe 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;
- L représente un groupe de formule -CO.NH-, -CO.NR³- ou -CO.O- ;
- R³ représente un groupe méthyle ou éthyle ; et
- Y représente un groupe phényle ; ou
- Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène ou triméthylène et Y¹ représente un groupe phényle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 1-isoquinolyle, 3-isoquinolyle, 4-isoquinolyle, 2-pyrimidinyle, 4-pyrimidinyle, 5-pyrimidinyle, 2-indolyle, 3-indolyle, 1-imidazolyle, 2-imidazolyle, 2-benzimidazolyle, 1-pyrazolyle, 3-pyrazolyle, 4-pyrazolyle, 3-indazolyle, 2-thiazolyle, 4-thiazolyle, 5-thiazolyle, 1,2,3-triazole-4-yle, 1,2,4-triazole-3-yle, 1,2,4-triazole-4-yle, 1,2,4-triazole-1-yle, 2-thiadiazolyle ou 5-tétrazolyle ; et
- chacun desdits groupes aryle ou hétéroaryle peut être non substitué ou bien peut porter un ou deux substituants choisis entre les groupes amino, nitro, carbamoyle, fluoro, méthyle, éthoxycarbonyle, méthylsulfinyle, méthylsulfonyle, méthoxy, trifluorométhyle et benzyle ;

ou un de ses sels pharmaceutiquement acceptables.

11. Quinazoline de formule I suivant la revendication 1, dans laquelle R¹ représente un groupe méthyle ; R² représente un groupe méthyle, éthyle ou prop-2-ynyle ; Ar représente un groupe 1,4-phénylène ou thién-2,5-diyle, ou représente un groupe pyrid-2,5-diyle ou thiazole-2,5-diyle, chacun avec le groupe -L-Y en position 2, ou bien représente un groupe 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CO.NH- et

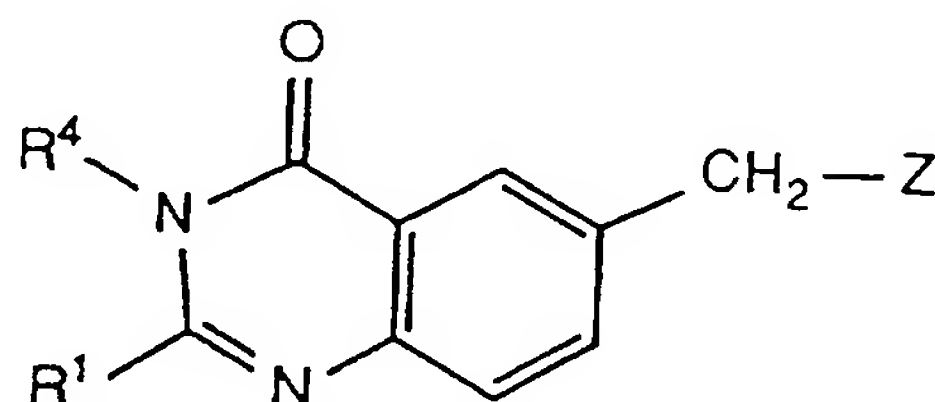
- Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène ou éthylène et Y¹ représente un groupe 2-pyridyle, 3-pyridyle, 4-pyridyle, 3-indolyle ou 1,2,4-triazole-1-yle, ou bien Y¹ représente un groupe phényle qui peut être non substitué ou qui peut porter un substituant choisi entre les groupes amino, nitro, éthoxycarbonyl et trifluorométhyle ;

ou un de ses sels pharmaceutiquement acceptables.

12. Quinazoline de formule I suivant la revendication 1, choisie dans le groupe de composés :
N-benzyl-p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]benzamide ;
p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)-benzamide ;
p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylméthyl)-benzamide ;
p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylméthyl)-benzamide, et
p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-éthylamino]benzoate de N-benzylimidazole-2-ylméthyle.

13. Procédé de production d'une quinazoline suivant l'une quelconque des revendications 1 à 12, qui comprend :

(a) la réaction d'un composé de formule II



II

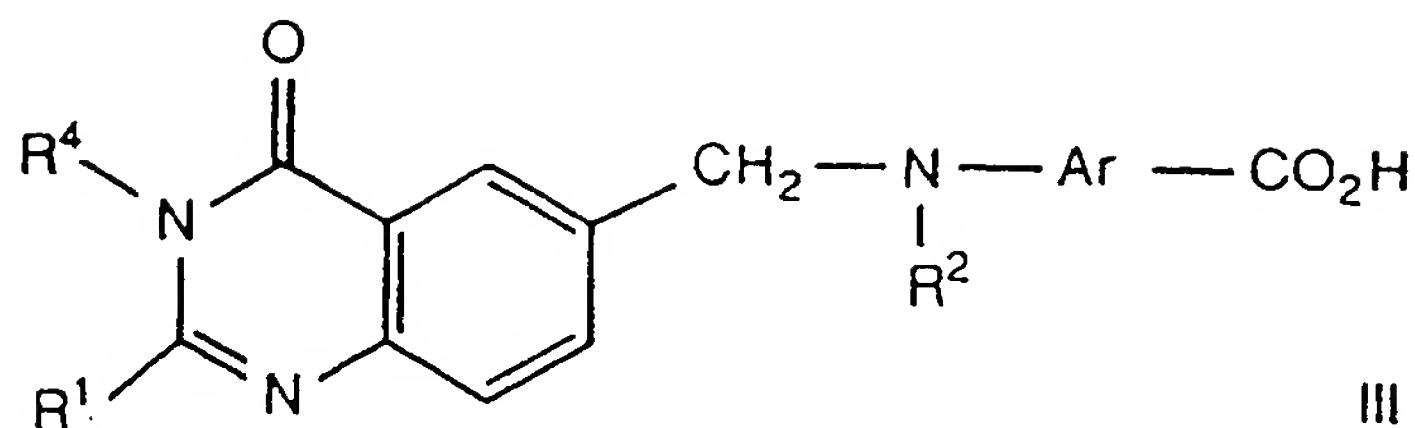
- dans laquelle R¹ répond à la définition suivant la revendication 1, sous réserve que, lorsque R¹ représente un groupe amino, hydroxyalkyle ou hydroxyalkoxy, n'importe quel groupe amino ou hydroxy soit protégé avec un groupe protecteur classique, R⁴ représente l'hydrogène ou un groupe protecteur et Z représente un groupe déplaçable, avec un composé de formule :

HNR²-Ar-L-Y

- dans laquelle R², Ar, L et Y répondent aux définitions suivant la revendication 1, sous réserve que, lorsqu'il existe un groupe amino, alkylamino, imino, hydroxy ou carboxy dans R², Ar, ou Y, n'importe quel groupe amino, alkylamino, imino ou carboxy soit protégé avec un groupe protecteur classique et n'importe quel groupe hydroxy puisse être protégé avec un groupe protecteur classique ou, en variante, n'importe quel groupe hydroxy ne nécessite pas une protection;

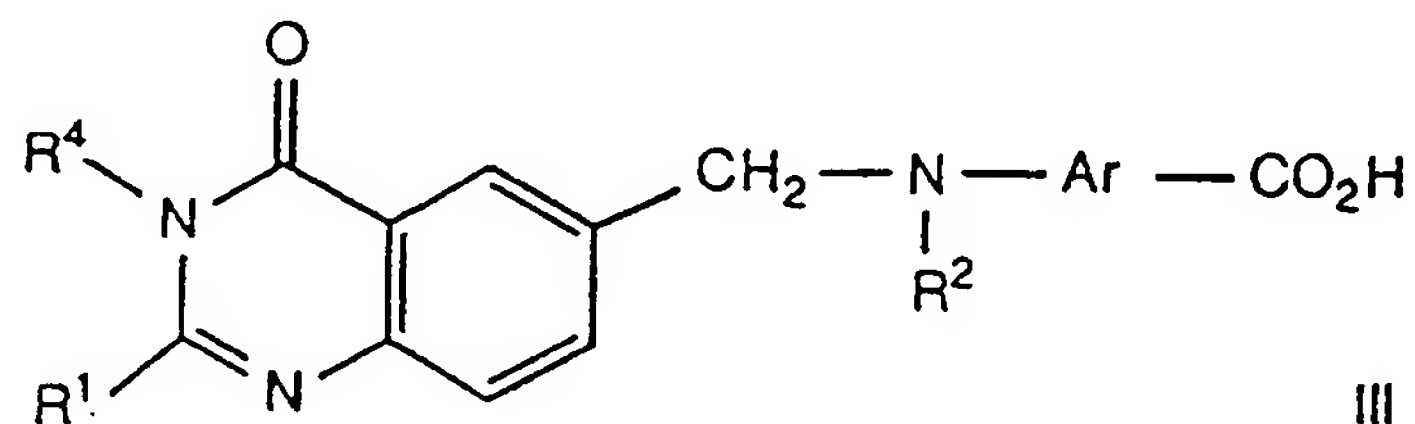
n'importe quel groupe protecteur non désiré dans R¹, R², Ar et Y étant ensuite éliminé ;

- (b) pour la production d'une quinazoline suivant la revendication 1 dans laquelle L représente un groupe de formule -CONH- ou -CONR³-, la réaction d'un acide de formule III, ou d'un de ses dérivés réactifs,



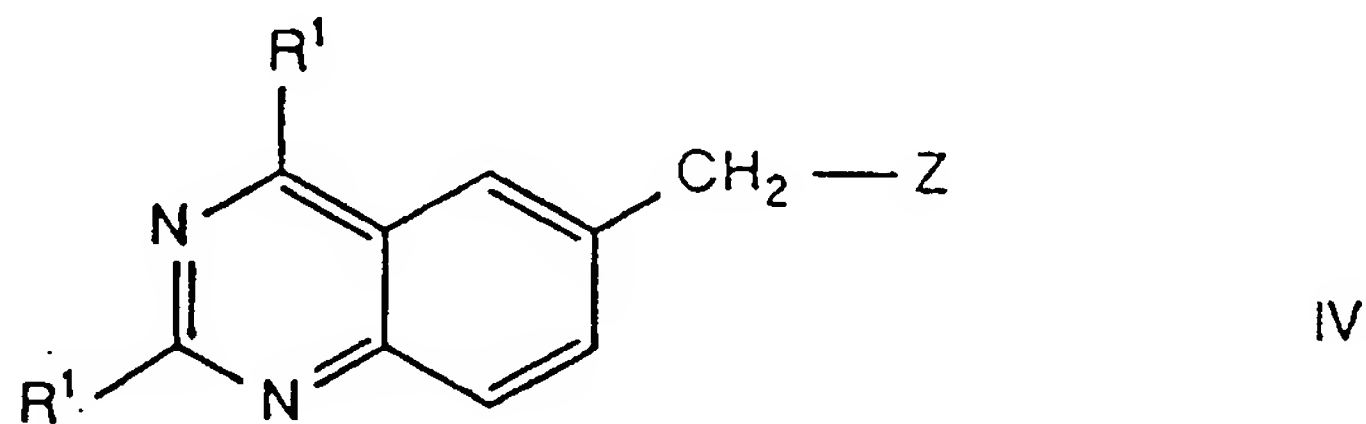
avec un composé de formule H_2N-Y ou R^3NH-Y , formules dans lesquelles R^1 , R^2 , R^3 , R^4 , Ar et Y répondent aux définitions suivant la revendication 1 et n'importe quel groupe amino, alkylamino, imino ou carboxy dans R^1 , Ar et Y est protégé avec un groupe protecteur classique et n'importe quel groupe hydroxy dans R^1 , R^2 , Ar et Y peut être protégé avec un groupe protecteur classique ou, en variante, n'importe quel groupe hydroxy ne nécessite pas une protection ; les groupes protecteurs étant ensuite éliminés par des moyens classiques ;

(c) pour la production d'une quinazoline suivant la revendication 1 dans laquelle L représente un groupe de formule $-CO.O-$, la réaction, en présence d'une base convenable, d'un acide de formule III, ou d'un de ses dérivés réactifs,

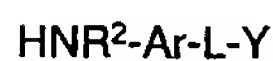


avec un composé de formule $HO-Y$, formules dans lesquelles R^1 , R^2 , R^3 , R^4 , Ar et Y répondent aux définitions suivant la revendication 1, et n'importe quel groupe amino, alkylamino, imino, hydroxy ou carboxy dans R^1 , R^2 , Ar et Y est protégé avec un groupe protecteur classique ; les groupes protecteurs étant ensuite éliminés par des moyens classiques ;

(d) pour la production d'une quinazoline suivant la revendication 1, dans laquelle R^1 représente un groupe alkoxy, hydroxyalkoxy ou alkoxyalkoxy, la réaction d'un composé de formule IV



dans laquelle R^1 répond à la définition mentionnée ci-dessus en dernier, sous réserve que, lorsqu'il existe un substituant hydroxy dans R^1 , ce substituant soit protégé avec un groupe protecteur classique, et Z représente un groupe déplaçable, avec un composé de formule :



dans laquelle R^2 , Ar, L et Y répondent aux définitions suivant la revendication 1, sous réserve que, lorsqu'il existe un groupe amino, alkylamino, imino, hydroxy ou carboxy dans R^2 , Ar ou Y, n'importe quel groupe amino, alkylamino, imino ou carboxy soit protégé avec un groupe protecteur classique et n'importe quel groupe hydroxy puisse être protégé avec un groupe protecteur classique ou, en variante, n'importe quel groupe hydroxy ne nécessite pas une protection ;

les groupes protecteurs étant ensuite éliminés par des moyens classiques,

et le groupe R¹ situé en position 4 du noyau quinazoline est clivé par hydrolyse avec une base ;
 (e) pour la production d'une quinazoline suivant la revendication 1 dans laquelle Y représente un
 groupe de formule -A-Y¹ dans laquelle un groupe méthylène constitutif dans A est remplacé par un
 groupe sulfinyle ou sulfonyle, ou dans laquelle il existe un substituant alkylsulfinyle ou alkylsulfonyle
 dans Y, l'oxydation d'un composé de formule I dans laquelle Y représente un groupe de formule -A-
 Y¹ dans laquelle A est remplacé par un groupe thio, ou dans laquelle il existe un substituant alkylthio
 dans Y ; et

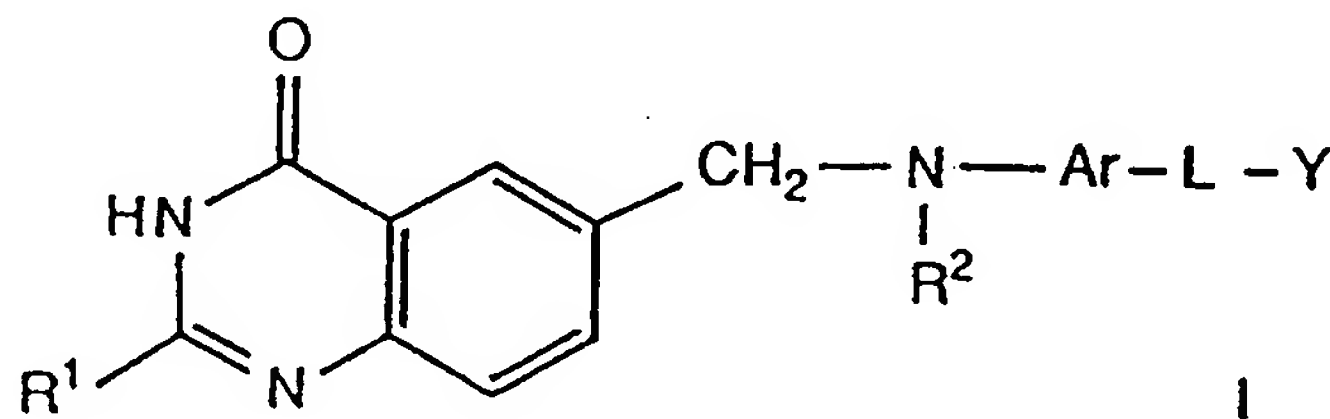
(f) pour la production d'une quinazoline suivant la revendication 1 dans laquelle il existe un
 substituant carboxy ou carboxyalkyle dans Y, le clivage d'un composé de formule I dans laquelle il
 existe un substituant alkoxy-carbonyl ou alkoxy-carbonylalkyle dans Y.

14. Composition pharmaceutique qui comprend une quinazoline suivant la revendication 1, ou un de ses
 sels pharmaceutiquement acceptables, en association avec un diluant ou support pharmaceutiquement
 acceptable.

15. Utilisation d'une quinazoline suivant la revendication 1, ou d'un de ses sels pharmaceutiquement
 acceptables, dans la production d'un médicament nouveau destiné à être utilisé dans la production
 d'un effet antitumoral chez un animal à sang chaud tel que l'homme.

20 Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de production d'une quinazoline de formule I



dans laquelle R¹ représente l'hydrogène ou un groupe amino, ou bien un groupe alkyle ou alkoxy ayant
 chacun jusqu'à 6 atomes de carbone ;

ou R¹ représente un groupe alkyle ayant jusqu'à 3 atomes de carbone qui porte un substituant
 hydroxy, ou bien qui porte 1, 2 ou 3 substituants fluoro ;

ou bien R¹ représente un groupe hydroxyalkoxy ayant jusqu'à 3 atomes de carbone ou alkoxyal-
 koxy ayant jusqu'à 6 atomes de carbone ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un
 substituant supplémentaire choisi entre un groupe halogéno et entre un groupe alkyle et un groupe
 alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

R² représente l'hydrogène, un groupe alkyle, alcényle, alcynyle, hydroxyalkyle, halogénalkyle ou
 cyanoalkyle ayant chacun jusqu'à 6 atomes de carbone ;

Ar représente un groupe phénylène ou hétérocyclène qui peut être non substitué ou bien qui peut
 porter un ou deux substituants choisis entre des groupes halogéno, hydroxy, amino et nitro, et entre
 des groupes alkyle, alkoxy et halogénalkyle ayant chacun jusqu'à 3 atomes de carbone ;

L représente un groupe de formule -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-,
 -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- ou -CO.O-, dans laquelle R³ représente un groupe alkyle
 ayant jusqu'à 6 atomes de carbone ; et

Y représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou
 bien un de ses dérivés hydrogénés ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe alkylène,
 cycloalkylène, alcénylène ou alcynylène ayant chacun jusqu'à 6 atomes de carbone, et Y¹ représente
 un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou bien un de ses
 dérivés hydrogénés ;

un groupe méthylène constitutif dans A peut être remplacé par un groupe oxy, thio, sulfinyle,
 sulfonyle ou imino ou un groupe alkylimino ayant jusqu'à 6 atomes de carbone ;

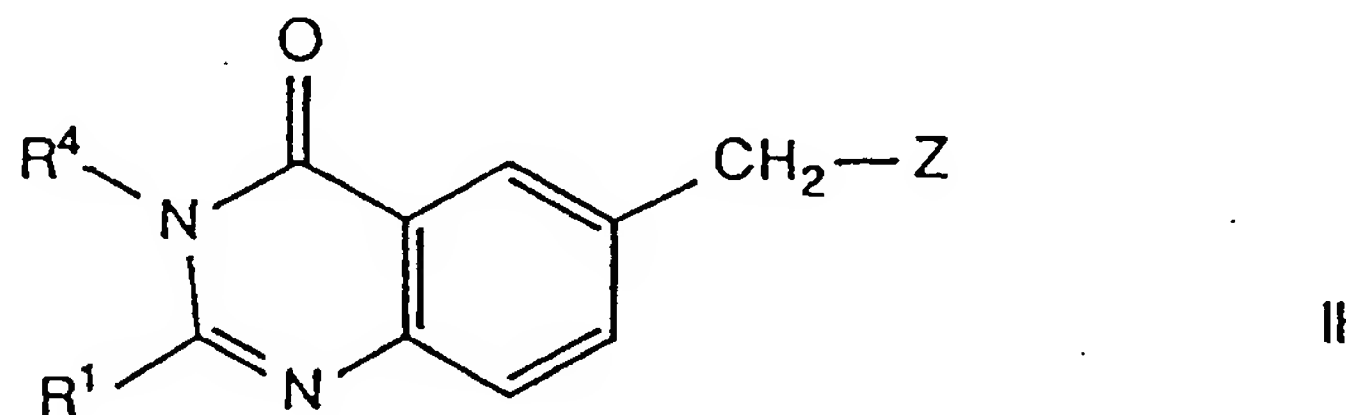
et chacun desdits groupes aryle ou hétéroaryle ou de leurs dérivés hydrogénés peut être non substitué ou pouvant porter jusqu'à trois substituants choisis entre des groupes hydroxy, oxo, amino, nitro, cyano, carbamoyle, sulfamoyle, carboxy et halogéno, entre des groupes alkyle, alkylamino, dialkylamino, N-alkylcarbamoyle, N,N-dialkylcarbamoyle, alkoxy-carbonyle, alcanoyloxyalkyle, alkylthio, alkylsulfinyle, alkylsulfonyle, alkoxy, halogénalkyle, hydroxyalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxyalkyle, alkoxy-carbonylalkyle, carbamoylalkyle, N-alkylcarbamoylalkyle et N,N-dialkylcarbamoylalkyle ayant chacun jusqu'à 6 atomes de carbone, et entre des groupes phényle, pyridyle et phénylalkyle ayant jusqu'à 10 atomes de carbone, et chacun desdits groupes phényle ou phénylalkyle peut porter un substituant choisi entre des substituants halogéno et nitro et entre des substituants alkyle et alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

ou d'un de ses sels pharmaceutiquement acceptables ;

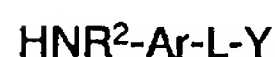
sous réserve que, lorsque R¹ représente l'hydrogène ou un groupe amino, ou bien un groupe alkyle ayant jusqu'à 6 atomes de carbone, et L représente un groupe de formule -CONH-, Y ne représente alors pas un groupe tétrazole ;

caractérisé par :

(a) la réaction d'un composé de formule II



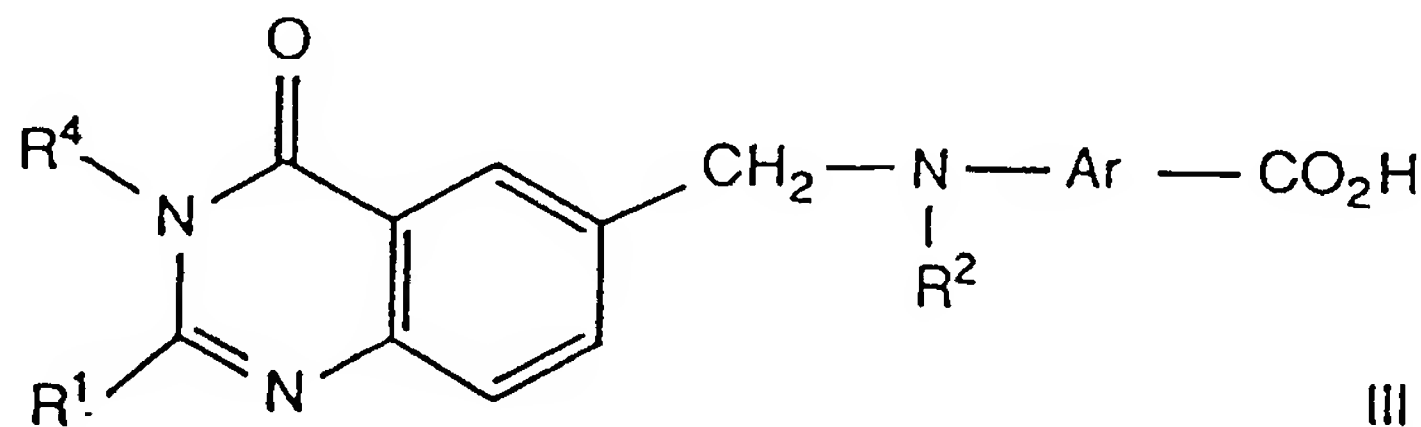
dans laquelle R¹ répond à la définition précitée, sous réserve que, lorsque R¹ représente un groupe amino, hydroxyalkyle ou hydroxyalkoxy, n'importe quel groupe amino ou hydroxy soit protégé avec un groupe protecteur classique, R⁴ représente l'hydrogène ou un groupe protecteur et Z représente un groupe déplaçable, avec un composé de formule :



dans laquelle R², Ar, L et Y répondent aux définitions précitées, sous réserve que, lorsqu'il existe un groupe amino, alkylamino, imino, hydroxy ou carboxy dans R², Ar, ou Y, n'importe quel groupe amino, alkylamino, imino ou carboxy soit protégé avec un groupe protecteur classique et n'importe quel groupe hydroxy puisse être protégé avec un groupe protecteur classique ou, en variante, n'importe quel groupe hydroxy ne nécessite pas une protection ;

n'importe quel groupe protecteur non désiré dans R¹, R², Ar et Y étant ensuite éliminé ;

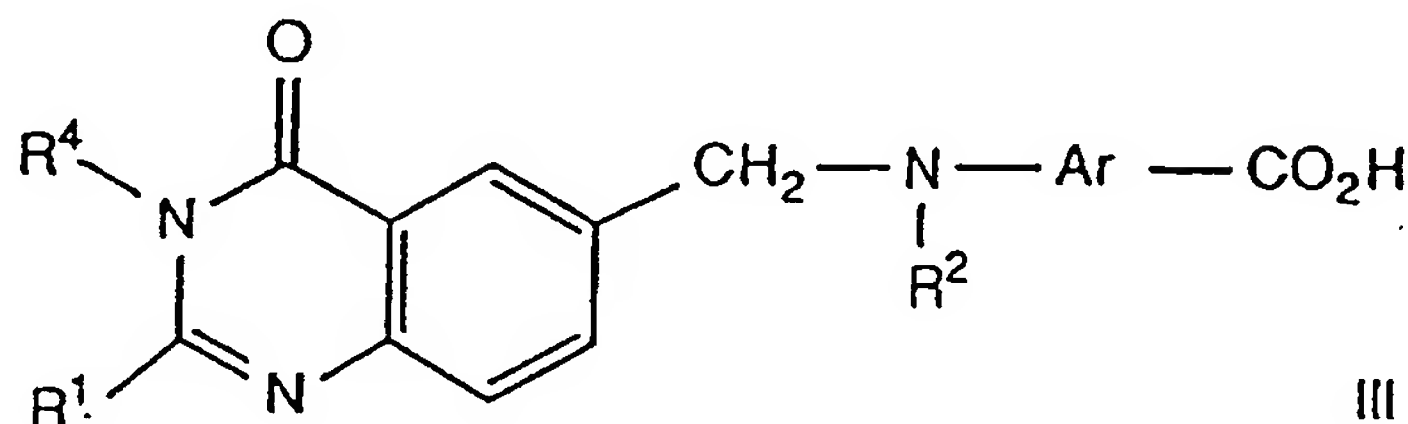
(b) pour la production d'une quinazoline de formule I dans laquelle L représente un groupe de formule -CONH- ou -CONR³-, la réaction d'un acide de formule III, ou d'un de ses dérivés réactifs,



avec un composé de formule H₂N-Y ou R³NH-Y, dans laquelle R¹, R², R³, R⁴, Ar et Y répondent aux définitions précitées et n'importe quel groupe amino, alkylamino, imino ou carboxy dans R¹, Ar et Y est protégé avec un groupe protecteur classique et n'importe quel groupe hydroxy dans R¹, R², Ar et Y peut être protégé avec un groupe protecteur classique, ou, en variante, n'importe quel groupe hydroxy ne nécessite pas une protection ; les groupes protecteurs étant ensuite éliminés par des

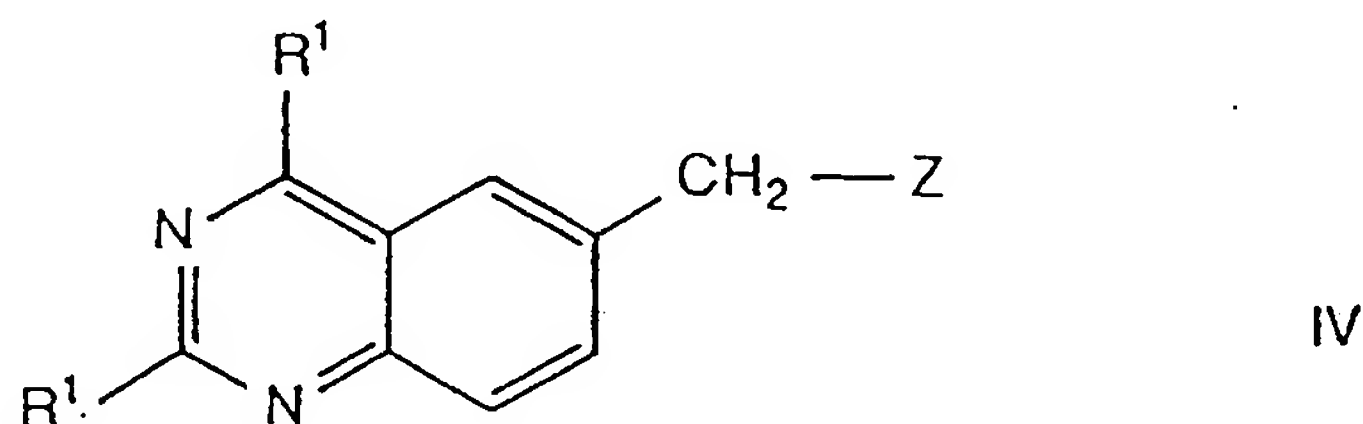
moyens classiques ;

(c) pour la production d'une quinazoline de formule I dans laquelle L représente un groupe de formule -CO.O-, la réaction, en présence d'une base convenable, d'un acide de formule III, ou d'un de ses dérivés réactifs,

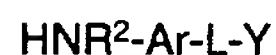


avec un composé de formule HO-Y, formules dans lesquelles R¹, R², R³, R⁴, Ar et Y répondent aux définitions précitées et n'importe quel groupe amino, alkylamino, imino, hydroxy ou carboxy dans R¹, R², Ar et Y est protégé avec un groupe protecteur classique ; les groupes protecteurs étant ensuite éliminés par des moyens classiques ;

(d) pour la production d'une quinazoline de formule I, dans laquelle R¹ représente un groupe alkoxy, hydroxyalkoxy ou alkoxyalkoxy, la réaction d'un composé de formule IV



dans laquelle R¹ répond à la définition mentionnée en dernier, sous réserve que, lorsqu'il existe un substituant hydroxy dans R¹, il soit protégé avec un groupe protecteur classique, et Z représente un groupe déplaçable, avec un composé de formule :



dans laquelle R², Ar, L et Y répondent aux définitions précitées, sous réserve que, lorsqu'il existe un groupe amino, alkylamino, imino, hydroxy ou carboxy dans R², Ar, ou Y, n'importe quel groupe amino, alkylamino, imino ou carboxy soit protégé avec un groupe protecteur classique et n'importe quel groupe hydroxy puisse être protégé avec un groupe protecteur classique, ou, en variante, n'importe quel groupe hydroxy ne nécessite pas une protection ;

les groupes protecteurs étant ensuite éliminés par des moyens classiques,

et le groupe R¹ situé en position 4 du noyau quinazoline est clivé par hydrolyse avec une base ;

(e) pour la production d'une quinazoline de formule I dans laquelle Y représente un groupe de formule -A-Y¹ dans laquelle un groupe méthylène constitutif dans A est remplacé par un groupe sulfinyle ou sulfonyle, ou dans laquelle il existe un substituant alkylsulfinyle ou alkylsulfonyle dans Y, l'oxydation d'un composé de formule I dans laquelle Y représente un groupe de formule -A-Y¹ dans laquelle A est remplacé par un groupe thio, ou dans laquelle il existe un substituant alkylthio dans Y ; et

(f) pour la production d'une quinazoline de formule I dans laquelle il existe un substituant carboxy ou carboxyalkyle dans Y, le clivage d'un composé de formule I dans laquelle il existe un substituant alkoxy-carbonyl ou alkoxy-carbonylalkyle dans Y.

2. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente l'hydrogène ou un groupe amino, ou bien un groupe méthyle, éthyle, méthoxy ou fluorométhyle ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

R² représente un groupe méthyle, éthyle, propyle, prop-2-ényle, prop-2-ynyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-fluoréthyle, 2-bromoéthyle ou cyanométhyle ;

5 Ar représente un groupe 1,4-phénylène, thiénylène, pyridylène, pyrimidinylène ou thiazolylène qui est non substitué ou qui porte un substituant choisi entre les groupes fluoro, chloro, bromo, hydroxy, amino, nitro, méthyle, méthoxy et trifluorométhyle ;

L représente un groupe de formule -CO.NH-, -CO.NR³- ou -CO.O-,

R³ représente un groupe méthyle ou éthyle ; et

10 Y représente un groupe phényle, 2,5-dioxopyrrolidinyle ou 2,6-dioxopipéridinyle, ou bien Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène, triméthylène, propylidène, propylène, butylidène, isobutylidène ou tétraméthylène et Y¹ représente un groupe phényle, furyle, thiényle, pyridyle, quinolyle, isoquinolyle, pyrazinyle, pyrimidinyle, quinazolinyle, pyridazinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, oxazolyle, isoxazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, tétrazolyle ou hexahydro-2-oxoazépin-1-yle ;

15 dans lequel un groupe méthylène constitutif dans A peut être remplacé par un groupe thio, sulfinyle, sulfonyle ou imino ; et

chacun desdits groupes phényle ou hétéroaryle, ou de leurs dérivés hydrogénés, peut être non substitué ou bien peut porter jusqu'à trois substituants choisis entre les groupes hydroxy, oxo, amino, nitro, cyano, carbamoyle, sulfamoyle, carboxy, fluoro, chloro, bromo, méthyle, éthyle, méthylamino, éthylamino, diméthylamino, diéthylamino, N-méthylcarbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, tertio-butyloxycarbonyle, isobutyryloxyméthyle, pivaloyloxyméthyle, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, méthylsulfonyle, éthylsulfonyle, méthoxy, éthoxy, trifluorométhyle, carboxyméthyle, 1-carboxyéthyle, 2-carboxyéthyle, 3-carboxypropyle, carbamoylméthyle, N-méthylcarbamoylméthyle, N,N-diméthylcarbamoylméthyle, phényle, pyridyle, benzyle, phénéthyle ou phénylpropyle, et n'importe quel groupe phényle à l'intérieur desdits substituants peut porter un substituant choisi entre les groupes fluoro, chloro, bromo, nitro, méthyle, éthyle, méthoxy et éthoxy ;

ou d'un de ses sels pharmaceutiquement acceptables.

30 3. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe amino, méthyle, méthoxy ou fluorométhyle ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

35 R² représente un groupe méthyle, éthyle, prop-2-ényle ou prop-2-ynyle ;

Ar représente un groupe 1,4-phénylène, thiénylène, pyridylène ou thiazolylène qui est non substitué ou qui porte un substituant fluoro ou nitro ;

L représente un groupe de formule -CO.NH- ou -CO.O- ; et

40 Y représente un groupe phényle, ou bien Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène, triméthylène, propylidène, propylène ou isobutylidène, et Y¹ représente un groupe phényle, 2-thiényle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 3-quinolyle, 4-quinolyle, 8-quinolyle, 2-pyrimidinyle, 4-pyrimidinyle, 6-quinazolinyle, 3-indolyle, 1-imidazolyle, 2-imidazolyle, 4-imidazolyle, 2-benzimidazolyle, 2-thiazolyle, 5-thiazolyle, 1,2,4-triazole-1-yle, 1,2,4-triazole-3-yle ou tétrazole-5-yle ou bien Y représente un groupe phénylsulfonyl ; et

45 chacun desdits groupes phényle ou hétéroaryle peut être non substitué ou bien peut porter jusqu'à trois substituants choisis entre les groupes hydroxy, oxo, amino, nitro, cyano, carbamoyle, carboxy, fluoro, chloro, méthyle, éthyle, N-méthylcarbamoyle, N,N-diméthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, pivaloyloxyméthyle, méthoxy, trifluorométhyle, carboxyméthyle, 1-carboxyéthyle, 2-carboxyéthyle, 3-carboxypropyle, 4-pyridyle et benzyle ;

50 ou d'un de ses sels pharmaceutiquement acceptables.

4. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe amino, méthyle ou méthoxy ;

le noyau quinazoline peut porter un substituant méthyle en position 7 ;

55 R² représente un groupe méthyle, éthyle ou prop-2-ynyle ;

Ar représente un groupe 1,4-phénylène ou thién-2,5-diyle, ou représente un groupe pyrid-2,5-diyle avec le groupe -L-Y en position 2, ou bien représente un groupe 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CONH- ;

et Y représente un groupe benzyle ou phénylsulfonyl qui peut porter un substituant nitro, cyano, carboxy ou trifluorométhyle, ou Y représente un groupe thiazole-5-ylméthyle ou 1,2,3,6-tétrahydro-2,6-dioxypyrimidin-4-ylméthyle, ou bien Y représente un groupe 2,3-dihydro-4-oxoquinazolin-6-ylméthyle qui peut porter un ou deux substituants méthyle ;

ou d'un de ses sels pharmaceutiquement acceptables.

5. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe méthyle ; le noyau quinazoline peut porter un substituant méthyle en position 7 ; R² représente un groupe méthyle ou prop-2-ynyle ; Ar représente un groupe 1,4-phénylène, ou 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CO.NH- ; et

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène et Y¹ représente un groupe 2-nitrophényle, 3-nitrophényle, 3-cyanophényle, 4-carboxyphényle ou 3-trifluorométhylphényle ou Y¹ représente un groupe 5-thiazolyle, 2,3-dihydro-4-oxoquinazolin-6-yle, 2,3-dihydro-2-méthyl-4-oxoquinazolin-6-yle ou 2,3-dihydro-2,3-diméthyl-4-oxoquinazolin-6-yle ;

ou d'un de ses sels pharmaceutiquement acceptables.

6. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I choisie dans le groupe de composés :

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-trifluorométhylbenzyl)benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(2-nitrobenzyl)-benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-méthylamino]-o-fluoro-N-(3-nitrobenzyl)-benzamide ;

5-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide ;

p-[N-(3,4-dihydro-2-méthoxy-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-benzamide ;

p-[N-(2-amino-3,4-dihydro-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-cyanobenzyl)-benzamide, et

p-[N-(3,4-dihydro-2,7-diméthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)-benzamide ;

ou un de ses sels pharmaceutiquement acceptables.

7. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe alkyle ou alkoxy ayant chacun jusqu'à 6 atomes de carbone ;

ou R¹ représente un groupe alkyle ayant jusqu'à 3 atomes de carbone qui porte un substituant hydroxy, ou qui porte un, deux ou trois substituants fluoro ;

ou bien R¹ représente un groupe hydroxyalkoxy ayant jusqu'à 3 atomes de carbone ou alkoxyalkoxy ayant jusqu'à 6 atomes de carbone ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre un groupe halogéno et un groupe alkyle et un groupe alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

R² représente l'hydrogène, un groupe alkyle, alcényle, alcynyle, hydroxyalkyle, halogénalkyle ou cyanoalkyle ayant chacun jusqu'à 6 atomes de carbone ;

Ar représente un groupe phénylène ou hétérocyclène qui peut être non substitué ou qui peut porter un ou deux substituants choisis entre des groupes halogéno, hydroxy et amino, et entre des groupes alkyle, alkoxy et halogénalkyle ayant chacun jusqu'à 3 atomes de carbone ;

L représente un groupe de formule -CO.HN-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CO.CH₂-, -CH₂.CO- ou -CO.O-, dans laquelle R³ représente un groupe alkyle ayant jusqu'à 6 atomes de carbone ; et

Y représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou

bien un de ses dérivés hydrogénés ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe alkylène, cycloalkylène, alcénylène ou alcynylène ayant chacun jusqu'à 6 atomes de carbone, et Y¹ représente un groupe aryle ayant jusqu'à 10 atomes de carbone, ou un groupe hétéroaryle ou bien un de ses dérivés hydrogénés ;

un groupe méthylène constitutif dans A peut être remplacé par un groupe oxy, thio, sulfinyle, sulfonyle ou imino ou un groupe alkylimino ayant jusqu'à 6 atomes de carbone ;

et chacun desdits groupes aryle ou hétéroaryle, ou de leurs dérivés hydrogénés, peut être non substitué ou bien peut porter un ou deux substituants choisis entre des groupes hydroxy, amino, nitro, cyano, carbamoyle, carboxy et halogéno, entre des groupes alkyle, alkylamino, dialkylamino, N-alkylcarbamoyle, N,N-dialkylcarbamoyle, alkoxy-carbonyl, alkylthio, alkylsulfinyle, alkylsulfonyl, alkoxy, halogénalkyle, hydroxyalkyle, aminoalkyle, alkylaminoalkyle, dialkylaminoalkyle, carboxyalkyle, alkoxy-carbonylalkyle, carbamoylalkyle, N-alkylcarbamoylealkyle et N,N-dialkylcarbamoylealkyle ayant chacun jusqu'à 6 atomes de carbone et entre des groupes phényle et phénylalkyle ayant jusqu'à 10 atomes de carbone, et chacun desdits groupes phényle peut porter un substituant choisi entre un groupe halogéno et entre un groupe alkyle et un groupe alkoxy ayant chacun jusqu'à 3 atomes de carbone ;

ou d'un de ses sels pharmaceutiquement acceptables ;

sous réserve que, lorsque R¹ représente un groupe alkyle ayant jusqu'à 6 atomes de carbone, le noyau quinazoline ne porte aucun substituant supplémentaire ou bien porte un substituant supplémentaire choisi entre un groupe halogéno et un groupe alkyle ayant jusqu'à 3 atomes de carbone,

R² représente un groupe alkyle, alcényle ou alcynyle ayant chacun jusqu'à 6 atomes de carbone,

Ar représente un groupe phénylène qui est non substitué ou bien qui porte un ou deux substituants choisis entre des groupes halogéno, hydroxy et amino, et

L représente un groupe de formule -CONH-, alors que Y ne représente pas un groupe tétrazole-5-yle.

8. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe méthyle, éthyle, méthoxy ou fluorométhyle ;

le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

R² représente l'hydrogène, un groupe méthyle, éthyle, propyle, prop-2-ényle, prop-2-ynyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-fluoroéthyle, 2-bromoéthyle ou cyanométhyle ;

Ar représente un groupe 1,4-phénylène, thiénylène, pyridylène, pyrimidinylène, thiazolylène ou thiadiazolylène qui est non substitué ou bien qui porte un ou deux substituants choisis entre les groupes fluoro, chloro, bromo, hydroxy, amino, méthyle, méthoxy et trifluorométhyle ; L représente un groupe de formule -CO.NH-, -NH.CO-, -CO.NR³-, -NR³.CO-, -CH=CH-, -CH₂O-, -CO.CH₂- ou -CO.O-, dans laquelle R³ représente un groupe méthyle ou éthyle ; et

Y représente un groupe phényle, naphtyle, pyridyle, quinolyle, isoquinolyle, pyrimidinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, oxazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, thiadiazolyle ou tétrazolyle ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène, triméthylène, propylidène, propylène, 1-isopropyléthylène ou tétraméthylène et Y¹ représente un groupe phényle, naphtyle, pyridyle, quinolyle, isoquinolyle, pyrazinyle, pyrimidinyle, pyridazinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, oxazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, thiadiazolyle ou tétrazolyle ;

un groupe méthylène constitutif dans A peut être remplacé par un groupe oxy, thio, sulfinyle ou sulfonyl ; et

chacun desdits groupes aryle ou hétéroaryle, ou d'un de ses dérivés hydrogénés, peut être non substitué ou bien peut porter un ou deux substituants choisis entre les groupes hydroxy, amino, nitro, cyano, carbamoyle, carboxy, fluoro, chloro, bromo, méthyle, éthyle, méthylamino, éthylamino, diméthylamino, diéthylamino, N-méthylcarbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, méthoxycarbonyl, éthoxycarbonyl, tertio-butoxycarbonyl, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, isopropylsulfinyle, méthylsulfonyl, éthylsulfonyl, isopropylsulfonyl, méthoxy, éthoxy, trifluorométhyle, carboxyméthyle, 2-carboxyéthyle, carbamoylméthyle, N-méthylcarbamoyleméthyle, N,N-diméthylcarbamoyleméthyle, phényle, benzyle, phénéthyle et phénylpropyle, et chacun desdits groupes phényle peut porter un substituant choisi entre les groupes fluoro, chloro, bromo, méthyle, éthyle, méthoxy et éthoxy ;

ou d'un de ses sels pharmaceutiquement acceptables ;

sous réserve que, lorsque R¹ représente un groupe méthyle ou éthyle, le noyau quinazoline ne porte aucun substituant supplémentaire ou bien porte un substituant supplémentaire choisi entre les groupes fluoro, chloro et méthyle ;

R² représente un groupe méthyle, éthyle, propyle, prop-2-ényle ou prop-2-ynyle,

5 Ar représente un groupe 1,4-phénylène qui est non substitué ou bien qui porte un ou deux substituants choisis entre les groupes fluoro, chloro, bromo, hydroxy et amino, et

L représente un groupe de formule -CONH-, alors Y ne représente pas un groupe tétrazole-5-yle.

9. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe méthyle, éthyle, méthoxy ou fluorométhyle ;

10 le noyau quinazoline peut ne porter aucun substituant supplémentaire ou bien peut porter un substituant supplémentaire choisi entre les groupes fluoro, chloro, méthyle et méthoxy ;

R² représente l'hydrogène, un groupe méthyle, éthyle, propyle, prop-2-ényle, prop-2-ynyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-fluoroéthyle, 2-bromoéthyle ou cyanométhyle ;

15 Ar représente un groupe 1,4-phénylène, thién-2,5-diyle, pyrid-2,5-diyle ou thiazole-2,5-diyle qui est non substitué ou bien qui porte un ou deux substituants choisis entre les groupes fluoro, chloro, hydroxy, amino et méthyle ;

L représente un groupe de formule -CO.NH-, -CO.NR³- ou -CO.O-, dans laquelle R³ représente un groupe méthyle ou éthyle ; et

20 Y représente un groupe phényle, pyridyle, pyrimidinyle, imidazolyle, thiazolyle ou 1,2,3-triazolyle ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène ou triméthylène et Y¹ représente un groupe phényle, naphtyle, pyridyle, quinolyle, isoquinolyle, pyrimidinyle, indolyle, imidazolyle, benzimidazolyle, pyrazolyle, indazolyle, thiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, thiadiazolyle ou tétrazolyle ; et

25 chacun desdits groupes aryle ou hétéroaryle peut être non substitué ou bien peut porter un ou deux substituants choisis entre les groupes amino, nitro, fluoro, méthyle, carbamoyle, N-méthylcarbamoyle, N,N-diméthylcarbamoyle, méthoxycarbonyle, éthoxycarbonyle, méthylsulfinyle, méthylsulfonyle, méthoxy, trifluorométhyle, et benzyle ;

30 ou d'un de ses sels pharmaceutiquement acceptables ;

10. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe méthyle ; R² représente l'hydrogène, un groupe méthyle, éthyle, prop-2-ynyle ou 2-fluoréthyle ;

35 Ar représente un groupe 1,4-phénylène ou thién-2,5-diyle, ou représente un groupe pyrid-2,5-diyle ou thiazole-2,5-diyle, chacun avec le groupe -L-Y en position 2, ou bien représente un groupe 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CO.NH-, -CO.NR³- ou -CO.O- ;

R³ représente un groupe méthyle ou éthyle ; et

40 Y représente un groupe phényle ; ou

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène, éthylène, éthylidène ou triméthylène et Y¹ représente un groupe phényle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 1-isoquinolyle, 3-isoquinolyle, 4-isoquinolyle, 2-pyrimidinyle, 4-pyrimidinyle, 5-pyrimidinyle, 2-indolyle, 3-indolyle, 1-imidazolyle, 2-imidazolyle, 2-benzimidazolyle, 1-pyrazolyle, 3-pyrazolyle, 4-pyrazolyle, 3-indazolyle, 2-thiazolyle, 4-thiazolyle, 5-thiazolyle, 1,2,3-triazolyle-4-yle, 1,2,4-triazole-3-yle, 1,2,4-triazole-4-yle, 1,2,4-triazole-1-yle, 2-thiadiazolyle ou 5-tétrazolyle ; et

45 chacun desdits groupes aryle ou hétéroaryle peut être non substitué ou bien peut porter un ou deux substituants choisis entre les groupes amino, nitro, carbamoyle, fluoro, méthyle, éthoxycarbonyle, méthylsulfinyle, méthylsulfonyle, méthoxy, trifluorométhyle et benzyle ;

50 ou d'un de ses sels pharmaceutiquement acceptables.

11. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule I dans laquelle R¹ représente un groupe méthyle ; R² représente un groupe méthyle, éthyle ou prop-2-ynyle ; Ar représente un groupe 1,4-phénylène ou thién-2,5-diyle, ou représente un groupe pyrid-2,5-diyle ou thiazole-2,5-diyle, chacun avec le groupe -L-Y en position 2, ou bien représente un groupe 2-fluoro-1,4-phénylène avec le groupe -L-Y en position 1 ;

L représente un groupe de formule -CO.NH- et

Y représente un groupe de formule -A-Y¹ dans laquelle A représente un groupe méthylène ou

éthylène et Y¹ représente un groupe 2-pyridyle, 3-pyridyle, 4-pyridyle, 3-indolyle ou 1,2,4-triazole-1-yle, ou bien Y¹ représente un groupe phényle qui peut être non substitué ou qui peut porter un substituant choisi entre les groupes amino, nitro, éthoxycarbonyl et trifluorométhyle ;
ou d'un de ses sels pharmaceutiquement acceptables.

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12. Procédé suivant la revendication 1 pour la production d'une quinazoline de formule choisie dans le groupe de composés :

N-benzyl-p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]benzamide ;

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p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(m-nitrobenzyl)-benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(2-pyridylméthyl)-benzamide ;

p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-(prop-2-ynyl)amino]-N-(3-pyridylméthyl)-benzamide, et

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p-[N-(3,4-dihydro-2-méthyl-4-oxoquinazolin-6-ylméthyl)-N-éthylamino]benzoate de N-benzylimidazole-2-ylméthyle.

13. Procédé pour la production d'une composition pharmaceutique, caractérisé par le mélange d'une quinazoline répondant à la définition suivant l'une quelconque des revendications 1 à 12, ou d'un de ses sels pharmaceutiquement acceptables, ou d'un diluant ou support pharmaceutiquement acceptable.

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14. Utilisation d'une quinazoline suivant l'une quelconque des revendications 1 à 12, ou d'un de ses sels pharmaceutiquement acceptables, dans la production d'un médicament nouveau destiné à être utilisé dans la production d'un effet antitumoral chez un animal à sang chaud tel que l'homme.

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